US Food and Drug Administration

Meeting of the Pulmonary-Allergy Drugs Advisory Committee

November 18, 2009

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Objective

- To discuss data submitted by the Applicant to support the safety and efficacy of Xolair for the treatment of asthma in patients 6 to 11 years of age with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids

Question 1 - Discussion

Xolair dosing is based on serum IgE levels. Discuss the implications (if any) of dosing that could result in an increase in circulating levels of omalizumab-IgE immune complexes in patients with IgE levels above 500 IU/mL.

Question 2 - Voting

Do the data provide substantial and convincing evidence that Xolair provides a clinically meaningful beneficial effect for the treatment of asthma in pediatric patients 6 to 11 years of age inadequately controlled despite the use of inhaled corticosteroids?

a) If not, what further efficacy data should be obtained?

Question 3 - Voting

Has the safety of Xolair been adequately assessed for the treatment of asthma in pediatric patients 6 to 11 years of age?

a) If not, what further safety data should be obtained?

Question 4 - Voting

Do the safety and efficacy data provide substantial and convincing evidence to support approval of Xolair for the treatment of asthma in patients 6 to 11 years of age with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids?

a) If not, what additional information is necessary to support approval?

Omalizumab (Xolair) - Efficacy and Safety and Post-marketing Commitments

- Adults and Adolescents 12 yrs and older

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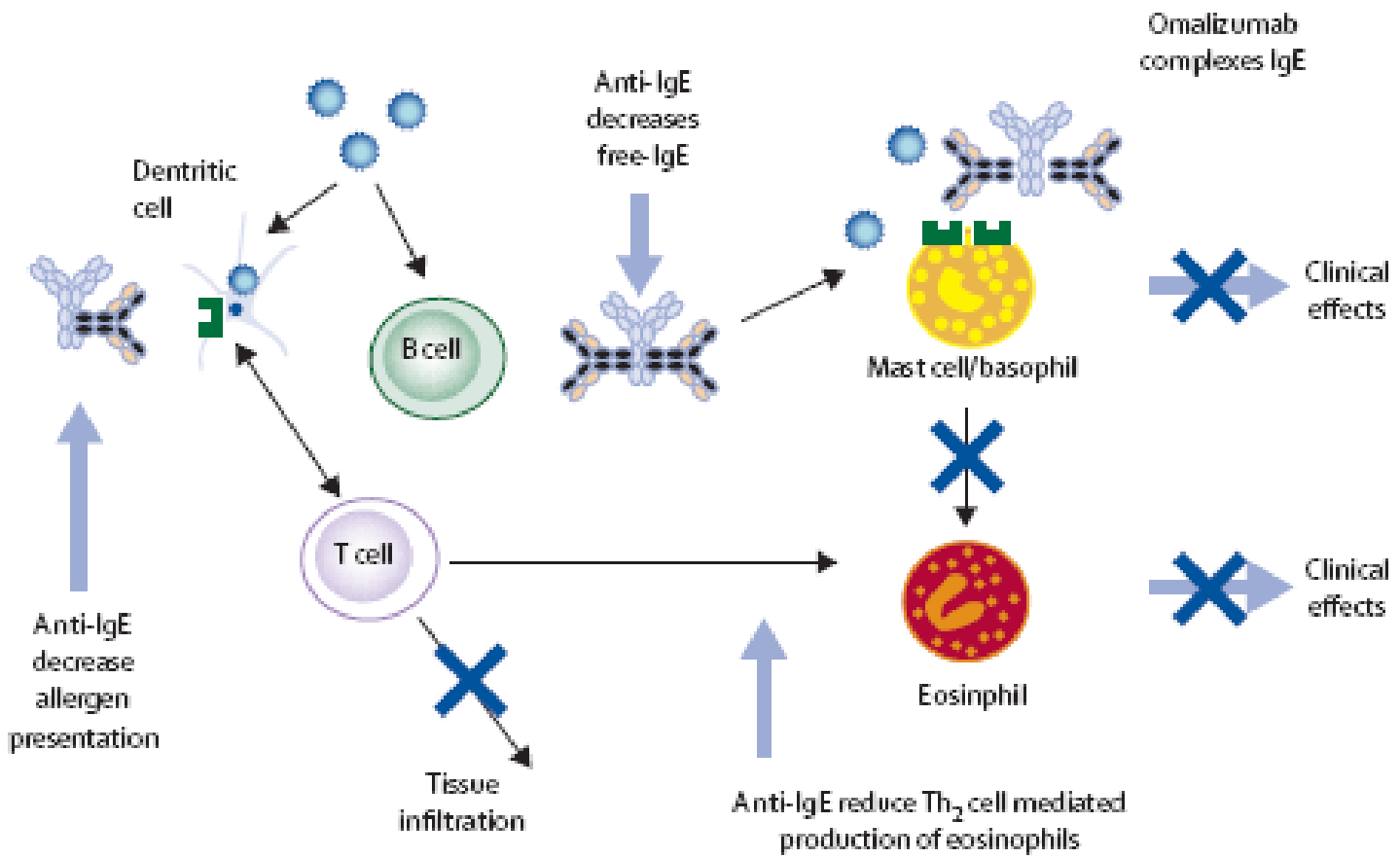
Omalizumab

Outline of Presentation

- Approved for marketing in the United States in June 2003
- Indication and Usage Studies: 1 or 008, 2 or 009, 3 or 011
  - For adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Dosage and Administration
  - 150 to 375 mg SC every 2 or 4 weeks
  - Determined by serum total IgE level (range ≥30 to 700 IU/mL), and body weight
- Safety – Warnings Studies: 1 or 008, 2 or 009, 3 or 011, ALTO
  - Anaphylaxis
  - Malignancy

Target of Anti-IgE



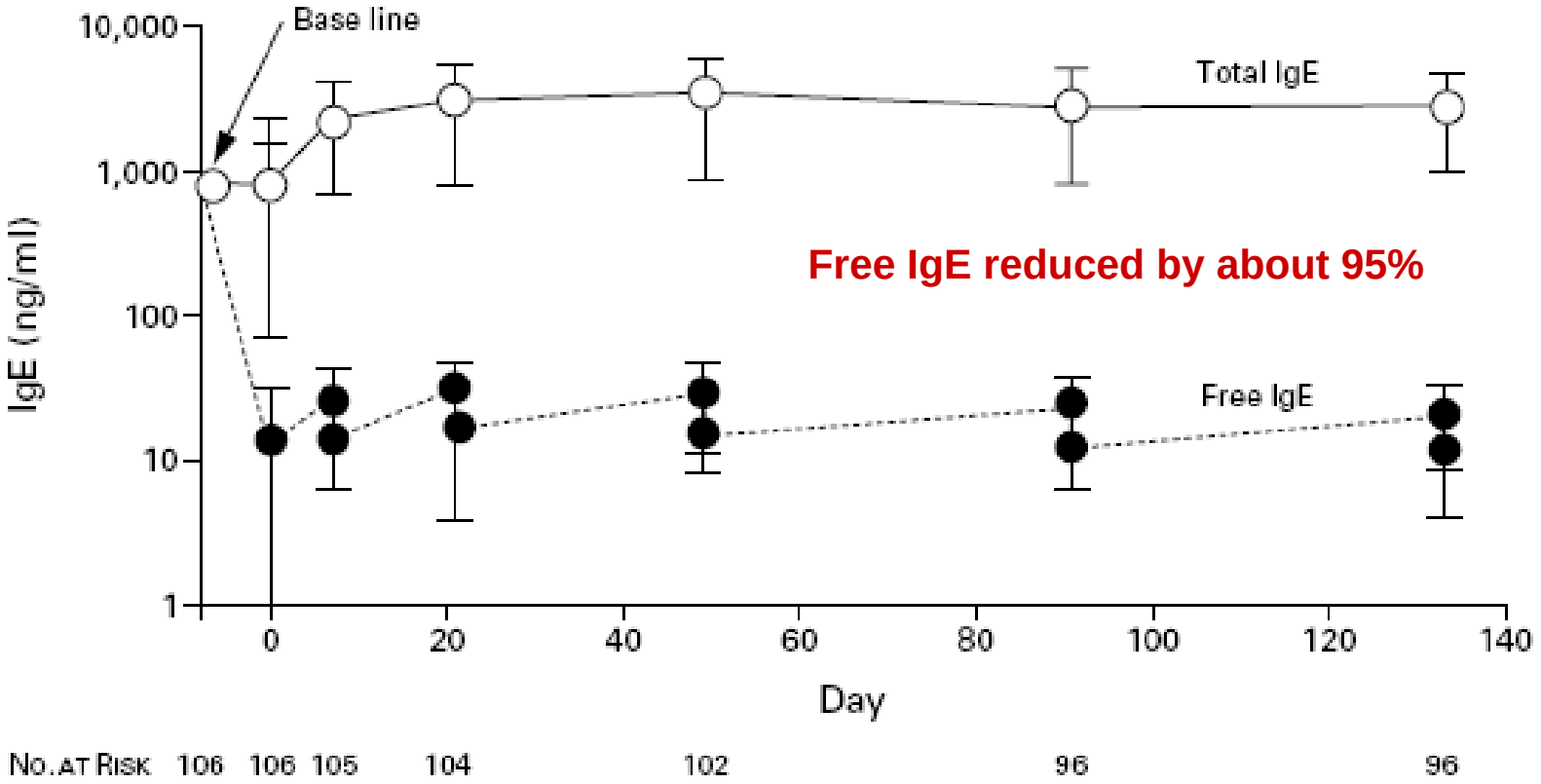
Lancet 2006; 368:780-793

Omalizumab
- Phase 2 Study

- Design
  - placebo-controlled, double-blind, dose-ranging
  - 4-wk run-in, followed by,
  - 12-wk treatment (2.5 or 5.8 mcg/kg body wt per ng IgE/mL; dosed IV every 2 weeks)
- Patients
  - age 11-50 yrs (n=317), FEV1 was 71% predicted, required inhaled or oral corticosteroids
- Primary endpoint
  - Change from baseline in a 7-point asthma symptom scale at week 12

NEJM 1999;341:1966-73

Omalizumab Phase 2 Study
- Serum IgE Concentration



NEJM 1999;341:1966-73

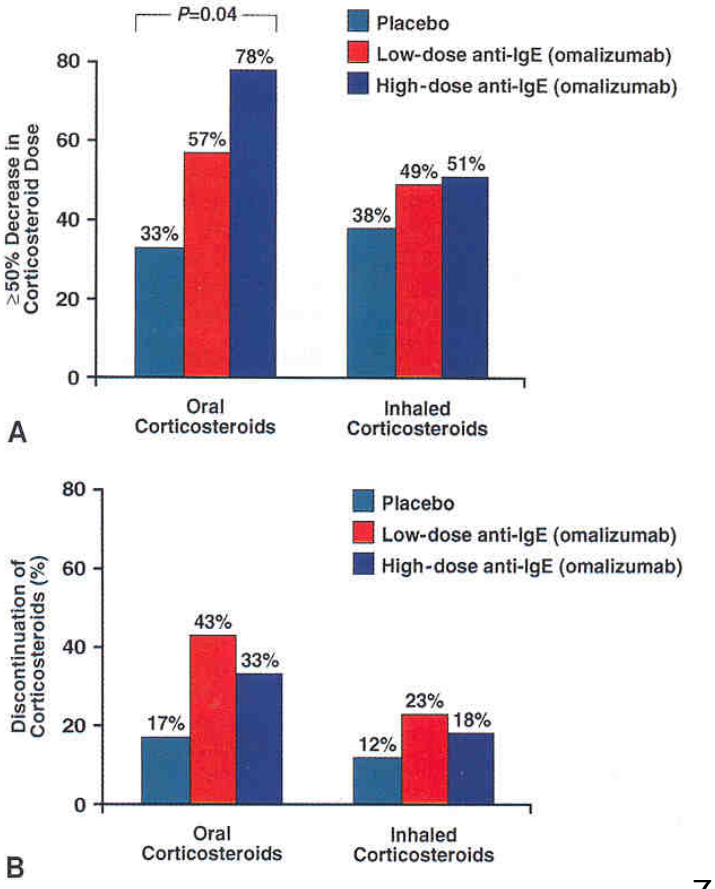
Omalizumab Phase 2 Study
- Change in Asthma Symptom Score

Score	High dose rhuMab-E25 (n=103)	Low dose rhuMab-E25 (n=103)	Placebo (n=100)
Baseline			
Mean ± SE	4.1 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Median	3.8	4.0	3.8
Week 12			
Mean ± SE	2.8 ± 0.1	2.8 ± 0.1	3.1 ± 0.1
P value	0.008	0.005	
>50% reduction in score number of subjects (%)	50 (49%)	50 (49%)	24 (24%)

NEJM 1999;341:1966-73

Omalizumab Phase 2 Study
- Secondary Efficacy Measures

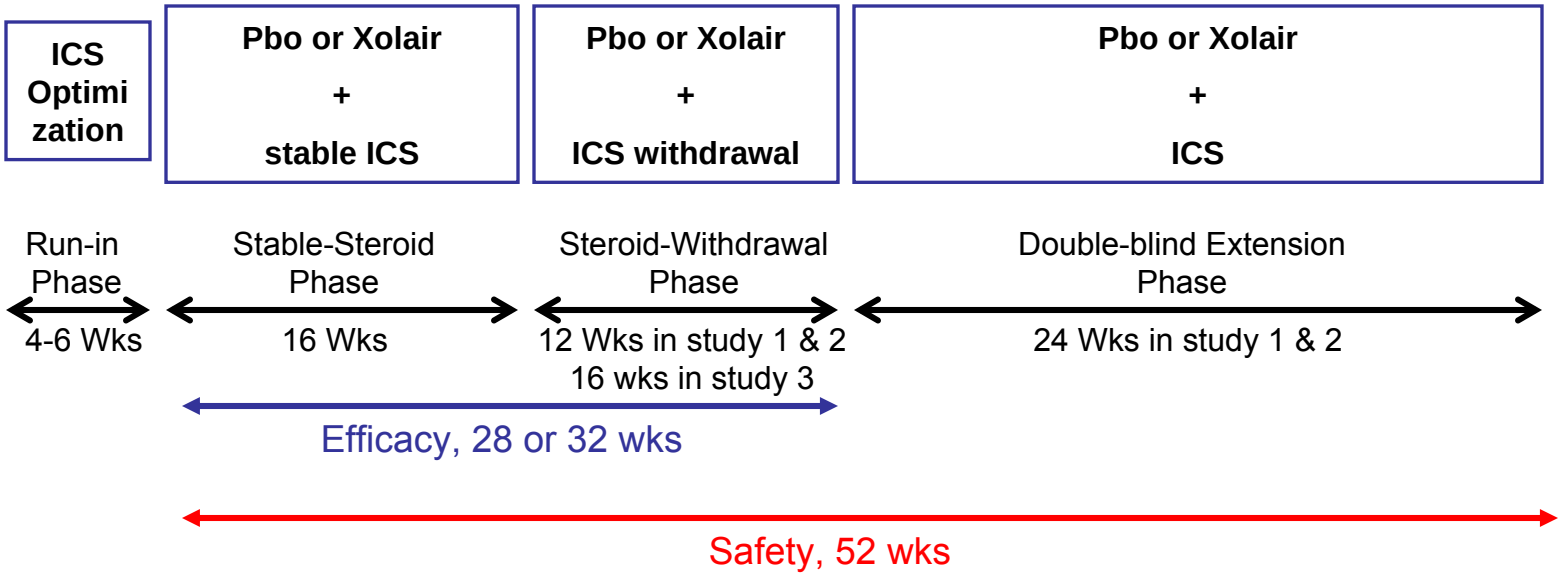
- More patients in the two omalizumab groups were able to discontinue corticosteroids compared to placebo group, but the differences were not consistently statistically significant.



NEJM 1999;341:1966-73

Omalizumab
Phase 3 Studies

- Efficacy and safety of Xolair was evaluated in 3 phase 3 studies
  - Study 1 or 008 (US): Busse et al; Allergy Clin Immunol 2001;108:184
  - Study 2 or 009 (US & International): Soler et al; Eur Respir J 2001;18:254
  - Study 3 or 011 (International): Holgate et al; Clin Exp Allergy 2004; 34:632



Am J Respir Crit Care Med 2001; 164:S12; Xolair Product Label

Omalizumab
Phase 3 Studies

- Patients (study 1 and 2)
  - 12-76 years old, moderate to severe persistent asthma for ≥1 year
  - Positive skin test to a perennial aeroallergen
  - FEV1 40-80% predicted
  - Baseline IgE 30-700 IU/mL, and body weight not more than 150 kg
- Patients (study 3)
  - 12-75 years old, moderate to severe persistent asthma for ≥1 year
  - Positive skin test to aeroallergen
  - No restriction on screening FEV1
  - Patients were on at least 1000 mcg/day inhaled fluticasone propionate and a subset was on oral steroids
  - Long-acting beta-agonists were allowed
  - Baseline IgE 30-700 IU/mL, and body weight not more than 150 kg

Am J Respir Crit Care Med 2001; 164:S12; Xolair Product Label

Omalizumab
Phase 3 Studies

- Primary endpoint (study 1 and 2)
  - Asthma exacerbation defined as “worsening of asthma requiring treatment with oral or intravenous corticosteroids or a doubling of the inhaled corticosteroid [beclomethasone] dose from baseline” during steroid-stable phase and steroid-withdrawal phase.
- Primary endpoint (study 3)
  - Percent reduction from baseline in inhaled corticosteroid [fluticasone] dose after 32 weeks treatment.

Am J Respir Crit Care Med 2001; 164:S12; Xolair Product Label

Omalizumab Studies 1 and 2
- Frequency of Asthma Exacerbations

	Stable Steroid Phase (16 weeks)			
	Study 1 (US)		Study 2 (US + Internationa)	
Exacerbations per patient	Xolair (n=268) %	Pbo (n=257) %	Xolair (n=274) %	Pbo (n=272) %
0	85.8	76.7	87.6	69.9
1	11.9	16.7	11.3	25.0
≥ 2	2.2	6.6	1.1	5.1
P-value	0.005		<0.001	
Mean no. exacer/patient	0.2	0.3	0.1	0.4

"Exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose"

Xolair Product Label

Omalizumab Studies 1 and 2
- Frequency of Asthma Exacerbations

	Steroid Reduction Phase (12 weeks)			
	Study 1 (US)		Study 2 (US + Internationa)	
Exacerbations per patient	Xolair (n=268) %	Pbo (n=257) %	Xolair (n=274) %	Pbo (n=272) %
0	78.7	67.7	83.9	70.2
1	19.0	28.4	14.2	26.1
≥ 2	2.2	3.9	1.8	3.7
P-value	0.004		<0.001	
Mean no. exacer/patient	0.2	0.4	0.2	0.3

"Exacerbation was defined as worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline ICS dose"

Xolair Product Label

Omalizumab Study 3
- Frequency of Asthma Exacerbations

	Stable Steroid Phase (16 weeks)			
	Inhaled Only		Oral + Inhaled	
	Xolair (n=126)	Pbo (n=120)	Xolair (n=50)	Pbo (n=45)
% Patients with ≥ 1 exacerbations	15.9	15.0	32.0	22.2
Difference (95% CI)	0.9 (-9.7, 13.7)		9.8 (-10.5, 31.4)	
	Steroid Reduction Phase (16 weeks)			
	Xolair (n=126)	Pbo (n=120)	Xolair (n=50)	Pbo (n=45)
% Patients with ≥ 1 exacerbations	22.2	26.7	42.0	42.2
Difference (95% CI)	-4.4 (-17.6, 7.4)		-0.2 (-22.4, 20.1)	

Xolair Product Label

Phase 3 Clinical Studies
- Quality-of-Life Outcome Analysis

- Asthma Quality of Life Questionnaire (AQLQ)
  - Comprises 32 items
  - Represent 4 domains (symptoms, emotions, exposure to environmental stimuli, activity limitations)
  - 7 point scale; 1=maximum improvement, 7=no improvement
- Responsiveness of AQLQ
  - 0.5 mean change is the minimally important difference, MID
  - 1.0 mean change represents a moderate change
  - 2.0 or greater change represents large change

J Clin Epidemiol 1994;47:81

AQLQ Results

Drug, Study, Phase of Study	Duration of study	n Drug, Pbo	Mean change over placebo from baseline to study end
Xolair, Study 1 or 008, Steroid Stable	16 wks	268, 257	0.53
Xolair, Study 1 or 008, Steroid Reduction	12 wks	268, 257	0.55
Xolair, Study 2 or 009, Steroid Stable	16 wks	274, 272	0.20
Xolair, Study 2 or 009, Steroid Reduction	12 wks	274, 272	0.32
Xolair, Study 3 or 011, Steroid Stable	16 wks	176, 165	0.23
Xolair, Study 3 or 011, Steroid Reduction	16 wks	176, 165	0.40

Ann Allergy Asthma Immunol 2006;96:316

AQLQ Results

Drug, Study, Phase of Study	Duration of study	n Drug, Pbo	Mean change over placebo from baseline to study end (95% CI)
Xolair, Study 1 or 008, Steroid Stable	16 wks	268, 257	0.53
Xolair, Study 1 or 008, Steroid Reduction	12 wks	268, 257	0.55
Xolair, Study 2 or 009, Steroid Stable	16 wks	274, 272	0.20
Xolair, Study 2 or 009, Steroid Reduction	12 wks	274, 272	0.32
Xolair, Study 3 or 011, Steroid Stable	16 wks	176, 165	0.23
Xolair, Study 3 or 011, Steroid Reduction	16 wks	176, 165	0.40
Advair Diskus 100/50	12 wks	87, 77	1.25
Advair HFA 45/21	12 wks	92, 87	1.14 (0.85, 1.44)
Symbicort 160/4.5	12 wks	124, 125	0.70 (0.47, 0.93)

Ann Allergy Asthma Immunol 2006;96:316; Product Labels

Omalizumab Phase 3 Studies - Efficacy Summary

- In studies 1 and 2 the number of exacerbations was reduced in patients treated with omalizumab compared with placebo
- In study 3 the number of exacerbations was similar in patients treated with omalizumab compared with placebo
- Hospitalization rates were not significantly different between omalizumab and placebo treated patients
- In all three of the studies, a reduction of asthma exacerbation was not observed in omalizumab treated patients
  - Who had FEV1 >80% at the time of randomization
  - Required oral steroids as maintenance therapy

Omalizumab

- Indication and Usage
  - For adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Dosage and Administration
  - 150 to 375 mg SC every 2 or 4 weeks
  - Determined by serum total IgE level (range ≥30 to 700 IU/mL), and body weight
- Safety – Warnings Studies: 1 or 008, 2 or 009, 3 or 011, ALTO
  - Anaphylaxis
  - Malignancy

Anaphylaxis with Omalizumab

- Warning in product label on approval
- In July 2007, changed to boxed warning, and added medication guide
- Based on
  - Pre-marketing controlled clinical studies
  - Post-marketing spontaneous adverse event reports

Xolair Product Label; www.fda.gov/cder/drug/infopage/omalizumab/default.htm

Anaphylaxis with Omalizumab
- Pre-marketing Controlled Studies

- 3 patients out of 3,507 had anaphylaxis
  - Based on investigator ascertainment
  - Onset 1.5 to 2 hours after dosing
  - Injection site reaction, hives, itching, throat and tongue swelling, dyspnea
  - Outpatient treatment with epinephrine, steroids, antihistamines
  - Omalizumab discontinued

Xolair (Omalizumab) Product Label; and May 15, 2003, PADAC (www.fda.gov/dockets/ac/acmenu.htm)

Anaphylaxis with Omalizumab
- Pre-marketing Controlled Studies

- 3 patients out of 3,507 had anaphylaxis
  - 28 year old female had injection site redness and edema, throat and tongue swelling, 2 hours after fourth SC dose (subj 11756, study Q2143g)
  - 19 year old female had hives, itching, and dyspnea, 1.5 hours after first SC dose (subj 12411, study Q2143g)
  - 30 year old male had “anaphylactoid” reaction 1.5 hours after first IV dose (subj 2712, study Q0694)

Xolair (Omalizumab) Product Label; and May 15, 2003, PADAC (www.fda.gov/dockets/ac/acmenu.htm)

Anaphylaxis with Omalizumab
- Pre-marketing Controlled Studies

- Study Q2143g (ALTO)
  - 6 month open label safety study in patients with asthma requiring ICS or OCS plus another drug (1261 omalizumab SC, 638 control)
  - Anaphylaxis
    - Omalizumab: 2
    - Control: 0
  - Urticaria with bronchospasm
    - Omalizumab: 5
    - Control: 0

Anaphylaxis with Omalizumab
- Post-marketing Spontaneous Reports

- Reporting Frequency
  - 124 unique cases of anaphylaxis reported from June 2003 to December 2006 (frequency of 0.2% based on exposure of 57,300 patients in the same time period)
- Life-threatening potential
  - 89% had pulmonary involvement
  - 14% had hypotension or syncope
  - 15% required hospitalization

Xolair (Omalizumab) Product Label; JACI 2007; 120:1378;
www.fda.gov/cder/drug/infopage/omalizumab/default.htm

Malignancy with Omalizumab
- Pre-marketing Controlled Studies

- Malignancy were observed in 20 of 4127 (0.5%) omalizumab treated patients compared with 5 of 2236 (0.2%) control patients in clinical studies of asthma and other allergic disorders.
- The observed malignancies in omalizumab treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once.
- The impact of longer exposure to omalizumab or use in patients with higher risk of malignancy is not known.

Xolair Product Label

Malignancy with Omalizumab
- Pre-marketing Controlled Studies

	Xolair (n=4127)	Placebo (n=2236)
Any	**20 (0.5%)**	**5 (0.2)**
Skin, non melanoma	**5**	**3**
Breast	**5**	**0**
Prostate	**2**	**0**
Melanoma	**2**	**0**
Parotid	**2**	**0**
Other	**5**	**2**

Xolair Product Label; and May 15, 2003, PADAC (www.fda.gov/dockets/ac/acmenu.htm)

Malignancy with Omalizumab
- Rates (events/1000 patient years)

	Xolair	Placebo	Rate ratio X/P (95% CI)
Any kind of malignancy	**6.3 20/3160**	**3.3 5/1513**	**1.9 (0.7, 6.5)**
Malignancy excluding non-melanoma skin cancer	**5.1 16/3160**	**1.3 2/1513**	**3.8 (0.9, 34.3)**

Xolair Product Label; and May 15, 2003, PADAC (www.fda.gov/dockets/ac/acmenu.htm)

Malignancy with Omalizumab
- Observed and Expected Malignancy

	Observed	Expected	SIR* (95% CI)
Xolair	**16**	**9**	**1.8 (1.0, 2.9)**
Placebo	**2**	**4.7**	**0.4 (0.1, 1.6)**

* SIR (Standardized Incidence Ratio): observed n / expected n

Expected n is from SEER (Surveillance, Epidemiology, and End Results) database that captures statistics from 14% of representative US population

Xolair Product Label; and May 15, 2003, PADAC (www.fda.gov/dockets/ac/acmenu.htm)

Malignancy with Omalizumab
- Post-marketing Spontaneous Reports

- 96 unique cases of malignancy reported from June 2003 to February 2009
- The observed malignancies in omalizumab treated patients were a variety of types, with breast, lung, prostate, ovarian, bone, brain, colon, thyroid, renal, bladder, skin, leukemia, and lymphoma occurring more than once

Omalizumab

- Indication and Usage
  - For adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who have positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with inhaled corticosteroids. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Dosage and Administration
  - 150 to 375 mg SC every 2 or 4 weeks
  - Determined by serum total IgE level (range ≥30 to 700 IU/mL), and body weight
- Safety – Warnings
  - Anaphylaxis
  - Malignancy
- Post-marketing commitment studies

Omalizumab PMC Studies

PMC 1	• A 28-week placebo-controlled, double-blind study in asthma patients with inadequate symptom control despite treatment with oral corticosteroids	**Efficacy study in severe persistent asthma**
PMC 2	• A placebo-controlled, double-blind study in asthma patients with FEV1 >80% who are receiving inhaled corticosteroids with or without concomitant long acting beta agonists	**Efficacy study in mild persistent asthma**
PMC 3	• An observational 5 year study of 5,000 Xolair treated and 2500 untreated patients to determine the incidence of malignancy and other serious adverse events	**Safety study assess serious safety risk**
PMC 4	• A study in 250 asthma patients to assess the stability of IgE levels in patients who discontinue Xolair treatment after treatment with Xolair for several months	**IgE stability study**
PMC 5	• A prospective, observational study of 250 pregnant women with asthma exposed to Xolair during pregnancy and breastfeeding	**Pregnancy registry**

PMC 1 (Q3662g)

- To conduct a multicenter, randomized, double-blind, parallel-group, placebo-controlled study with a 28-week treatment phase, to determine the effect of subcutaneous administration of omalizumab compared with placebo, on rates of clinically significant asthma exacerbations in adolescents and adults with asthma and skin test or *in vitro* reactivity to an aeroallergen who have reduced lung function and inadequate asthma symptom control despite treatment with oral corticosteroids.

Milestone	Commitment	Proposed Revised Dates	Completion Date
Submission of Final Protocol	June 30, 2004	NA	December 14, 2004
Completion of Accrual	September 30, 2006	NA	NA
Completion of Trial	February 28, 2007	December 31, 2008	NA
Submission of FSR to FDA	August 31, 2007	June 30, 2009	NA

All 850 subjects have been enrolled and 492 have completed

Status of the PMC on FDA web site: Delayed

PMC 2 (Q2982g)

- To conduct a parallel group, double blind, randomized and placebo controlled study, to assess the efficacy of omalizumab for the reduction of clinically significant exacerbations in asthma patients with an FEV1 ≥80% predicted who are receiving inhaled corticosteroids with our without concomitant long acting beta agonist use. These patients will have skin test or *in vitro* reactivity to an aeroallergen.

Milestone	Commitment	Proposed Revised Dates	Completion Date
Submission of Final Protocol	November 30, 2003	NA	February 20, 2004
Completion of Accrual	October 31, 2004	February, 2007	NA
Completion of Trial	June 30, 2005	August 2007	NA
Submission of FSR to FDA	November 30, 2005	April 2008	NA

Enrollment began December 2005. As of February 2009, 80 of 300 enrolled.
In 2009 Genentech proposed a meta-analysis of previous studies to fulfill this PMC. The Agency rejected this proposal.
Status of the PMC on FDA web site: Delayed

PMC 3 (Q2948g)

- To conduct a prospective, observational cohort study of 5,000 omalizumab treated and 2,500 untreated patients that assess the clinical safety of omalizumab by determining the incidence of malignancy and other serious adverse events (SAEs) in omalizumab treated patients with moderate to severe persistent asthma and skin test or *in vitro* reactivity to an aeroallergen compared with patients not treated with omalizumab. Study subjects will be followed for at least 5 years, and omalizumab treated patients will be matched at enrollment to untreated patients by age, gender, and race/ethnicity. Interim reports will be filed yearly.

Milestone	Commitment	Proposed Revised Dates	Completion Date
Submission of Final Protocol	December 31, 2003	NA	December 24, 2003
Completion of Accrual	March 31, 2006	NA	NA
Completion of Trial	March 31, 2011	June 30, 2011	NA
Submission of FSR to FDA	September 30, 2011	December 31, 2011	NA

Patient accrual completed in November 2006.

Status of the PMC on FDA web site: Ongoing.

PMC 3 (Q2948g)

- "Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS)"
  - Observational study
  - Plan is to follow 5000 omalizumab patients and 2500 non-omalizumab patients for 5 years
  - Study is ongoing
- Interim safety finding showed disproportionate increase in cardiovascular and cerebrovascular events in patients treated with omalizumab compared to control group (www.fda.gov/safety/MedWatch/SafetyInformation/SafetyAlertforHumanMedicalProducts/ucm172406.htm)

PMC 3 (Q2948g) – EXCELS

Interim results - cardiovascular and cerebrovascular SAEs

	Omalizumab cohort		Non-omalizumab cohort	
	No of events	Rate events/1000 pt yr, 95%CI	No of events	Rate events/1000 pt yr, 95%CI
Ischemic heart disease	35	3.1 (2.2, 4.3)	13	2.1 (1.1, 3.5)
Cardiac arrhythmias	37	3.3 (2.3, 4.5)	10	1.6 (0.8, 2.9)
Cardiomyopathy and cardiac failure	16	1.4 (0.8, 2.3)	5	0.8 (0.3, 1.9)
Pulmonary hypertension	6	0.5 (0.2, 1.2)	0	0
Cerebrovascular disorders	16	1.4 (0.8, 2.3)	3	0.5 (0.1, 1.4)
Embolic, thrombotic, and thrombophlebitic events	49	4.4 (3.2, 5.8)	18	2.9 (1.7, 4.5)

PMC 3 (Q2948g) - EXCELS

- This study unlikely to address the malignancy concern of omalizumab
  - Observational design of the study
  - Exclusion of patients with histories of cancers
    - Protocol amendment in 2005 removed this exclusions
  - Enrollment of patients who had already been on omalizumab
  - No minimal duration of exposure to omalizumab

Randomized Omalizumab Study Patients - 12 years and Older and 12 to <18 Years of Age

	Adults and adolescents 12 years and older		Adolescents 12 to <18 years of age	
	Omalizumab	**Placebo**	**Omalizumab**	**Placebo**
Study 1 or 008	268	257	20	21
Study 2 or 009	274	272	18	17
Study 3 or 011	176	165	12	9
Study ALTO or Q2143g	1221	620	82	44
All studies above	**1939**	**1314**	**132**	**91**

Efficacy and Safety of Xolair (omalizumab) in children 6-11 years of age with allergic asthma

Peter Starke, MD, FAAP
Division of Pulmonary and Allergy Products
Center for Drug Evaluation and Research
US Food and Drug Administration

Overview

- Overview of pediatric studies and program
- Proposed dosing schema
- Efficacy considerations
  - Study design and population
  - Primary variable and endpoint
  - Efficacy results
- Safety
- Summary

Pediatric development program: Controlled asthma trials in children 6-11 years of age

Study	Design	N 6-11y (total N)	Endpoint
Pivotal study			
IA05 US + ex-US	R, DB, PC efficacy, safety, and PK study in patients 6-11y with moderate-severe AA and continued symptoms despite ICS equivalent to FP ≥200μ/d ● 52 weeks of DB treatment ● 16 weeks of untreated FU	628: Xolair 421 Pbo 207	1°: Rate of clinically significant asthma exacerbations over 24 weeks of stable treatment
Supportive study			
010 US	Safety and tolerability study in patients 6-12 years with AA stable on ICS with ● Core: 7 months of randomized, DB, PC treatment, followed by: ● 5 months of OL treatment extension, ● 12 weeks of untreated FU	Core: 298 (334: Xolair 225, Pbo 109)	1°: Safety % reduction of ICS use, asthma exacerbations

Limitations of the program

- No evaluation of Xolair treatment compared to an increase in inhaled corticosteroid (ICS) dose
- No evaluation of when it may be appropriate to stop therapy
- No exploration of dose-response

Approved Xolair dosing schedule, ≥12 years

Dosing Interval	Baseline IgE (IU/mL)	Body Weight (kg)			
		30-60	>60-70	>70-90	>90-150
Q4wks	≥30-100	150	150	150	300
	>100-200	300	300	300	225
	>200-300	300	225	225	300
Q2wks	>300-400	225	225	300	DO NOT USE
	>400-500	300	300	375	
	>500-600	300	375		
	>600-700	375			

Source: Last approved Xolair package insert, Tables 5 and 6, 7/2/2007

Proposed Xolair dosing schedule, 6-11y

Dosing Interval	Baseline IgE (IU/mL)	Body Weight (kg)									
		20-25	>25 -30	>30- 40	>40- 50	>50- 60	>60- 70	>70- 80	>80- 90	>90- 125	>125- 150
Q4wks	≥30-100	75	75	75	150	150	150	150	150	300	300
	>100-200	150	150	150	300	300	300	300	300	225	300
	>200-300	150	150	225	300	300	225	225	225	300	375
	>300-400	225	225	300	225	225	225	300	300		
	>400-500	225	300	225	225	300	300	375	375		
	>500-600	300	300	225	300	300	375				
	>600-700	300	225	225	300	375					
Q2wks	>700-800	225	225	300	375						
	>800-900	225	225	300	375						
	>900-1000	225	300	375							
	>1000-1100	225	300	375							
	>1100-1200	300	300								
	>1200-1300	300	375								

Do not dose in this area

Dose	# of Injections	Total Volume (mL)*
75	1	0.6
150	1	1.2
225	2	1.8
300	2	2.4
375	3	3.0

*1.2 mL maximum volume/vial

Total Omalizumab-IgE Complex Exposure

- Circulating immune complex exposure in children with baseline IgEs ≥500 IU/mL is higher than in adults/adolescents with IgEs up to 700 IU/mL

Baseline IgE (IU/mL)	**Total Omalizumab-IgE (ng/mL)**	
	Pediatric Median (5-95 %ile)	**Adult** Median (5-95 %ile)
500-700	**3883** (1832-6844)	**3446** (1115-5496)
>700	**4060** (2380-7423)	NR

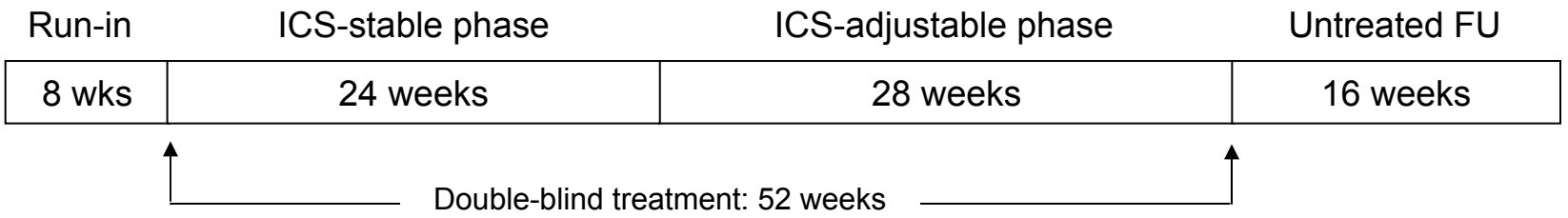
- In IA05 follow-up, levels of circulating complexes 4 months after stopping therapy had diminished, but were still present, and were about the same as after the first Xolair dose

Proposed Xolair dosing schedule, 6-11y

Dosing Interval	Baseline IgE (IU/mL)	Body Weight (kg)									
		20-25	>25 -30	>30- 40	>40- 50	>50- 60	>60- 70	>70- 80	>80- 90	>90- 125	>125- 150
Q4wks	≥30-100	75	75	75	150	150	150	150	150	300	300
	>100-200	150	150	150	300	300	300	300	300	225	300
	>200-300	150	150	225	300	300	225	225	225	300	375
	>300-400	225	225	300	225	225	225	300	300		
	>400-500	225	300	225	225	300	300	375	375		
	>500-600	300	300	225	300	300	375				
	>600-700	300	225	225	300	375					
Q2wks	>700-800	225	225	300	375						
	>800-900	225	225	300	375						
	>900-1000	225	300	375							
	>1000-1100	225	300	375							
	>1100-1200	300	300								
	>1200-1300	300	375								

The clinical meaning of higher circulating immune complexes is unknown

IA05



- Primary endpoint: Exacerbation rate over 24 weeks
- Secondary endpoints
  - Exacerbation rate over 52 weeks
  - Nocturnal symptom scores over 24 weeks
  - Asthma rescue medication use over 24 weeks
  - PAQLQ* score, Week 24
- Exploratory endpoints (24/52 weeks)
  - Time to first exacerbation, FEV1, % predicted FEV1, PEF, daytime and nighttime symptom scores, care utilization and hospitalizations, days of school or caregiver work missed, patient reported outcomes, ICS dose

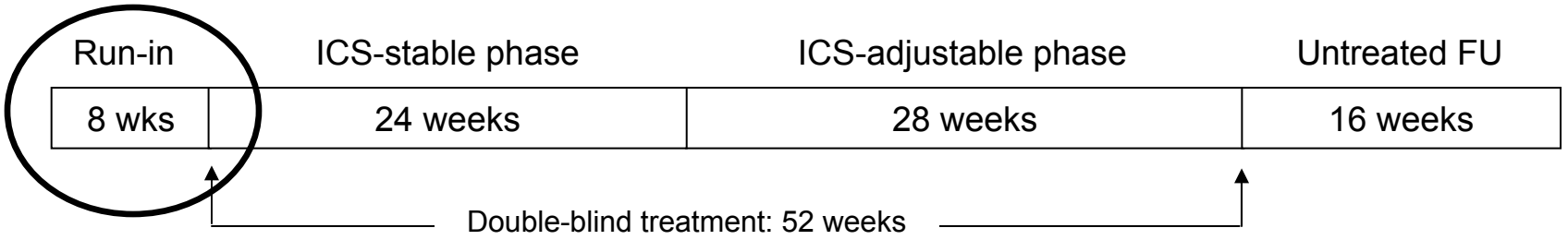
*PAQLQ = Pediatric Asthma Quality of Life Questionnaire

IA05: Study Population

- 6-11 years, moderate to severe persistent asthma ≥1y
- Positive skin test to perennial allergen
- ≥12% increase in FEV1 after beta-agonist
- Medium dose ICS: FP ≥200 mcg/day or equivalent, consistent with NAEPP Steps 3 or 4*
- Documented history of exacerbations
  - 2 w/in 12mo,
  - 3 w/in 24mo with 1 w/in 12mo, or
  - Hosp or ER visit with asthma w/in 12mo

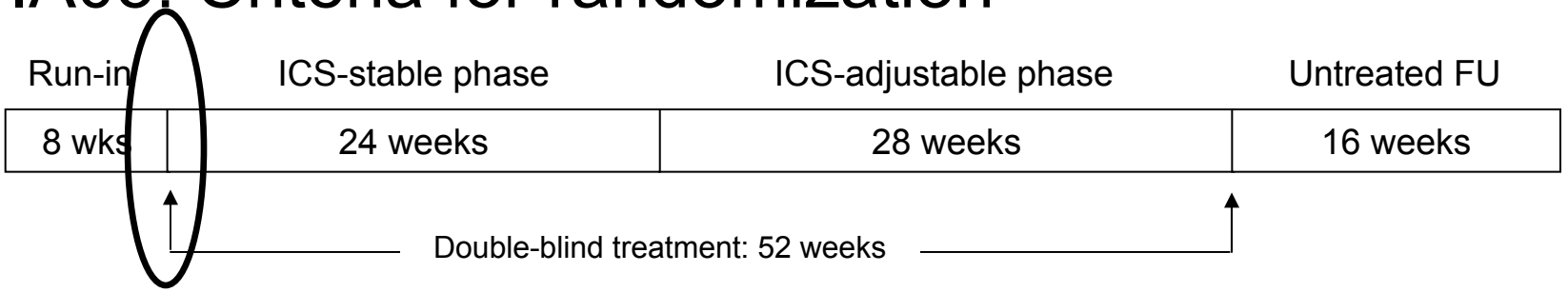
* NHLBI National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma (1997, update 2002)

IA05



- First 4 weeks: ICS and other asthma therapy “optimized”
  - ↑ ICS
  - Addition of other controllers, except LABA
- Last 4 weeks: No changes to asthma therapy

IA05: Criteria for randomization



- Evidence of inadequate symptom control during last 4 weeks of run-in
  - Daytime asthma symptom score ≥1 on ≥ 20 of 28 and a mean symptom score of 1.5, **and/or**
  - Night-time asthma awakening requiring rescue medication >4 times

IA05: Patient population (means for MITT[1])

- FEV1 % predicted = 85.4%
- FP equivalent ICS dose = 532 mcg/day (range: 119-1880)
- LABAs = 66%
- Anti-leukotriene therapy = 39%
- Exacerbation history = 2.6 per year[2]

1 MITT = Modified Intent to Treat population

2 Historical exacerbations were defined similarly to primary variable

IA05: Primary variable

- Primary variable: Clinically significant asthma exacerbations, defined as *investigator judged* worsening of asthma symptoms requiring a 2x of baseline ICS dose and/or rescue systemic corticosteroids for 3 days

- Based on:
  - Investigator judgment
  - Treatment, rather than the underlying reason (i.e., signs, symptoms, or objective measures) that prompted treatment

IA05: Primary efficacy results, MITT

	Xolair N=384	Placebo N=192
Asthma exacerbation rate, 24-week fixed-ICS phase	**0.45**	**0.64**
	RR=0.693 (0.533, 0.903), p=0.007	
Frequency of exacerbations	n (%)	n (%)
0	247 (64.3)	112 (58.3)
1 or more	137 (35.7)	80 (41.7)
1	86 (22.4)	41 (21.4)
2	38 (9.9)	23 (12.0)
3	9 (2.3)	12 (6.3)
≥4	4 (1.0)	4 (2.1)

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Sub-analyses of primary endpoint

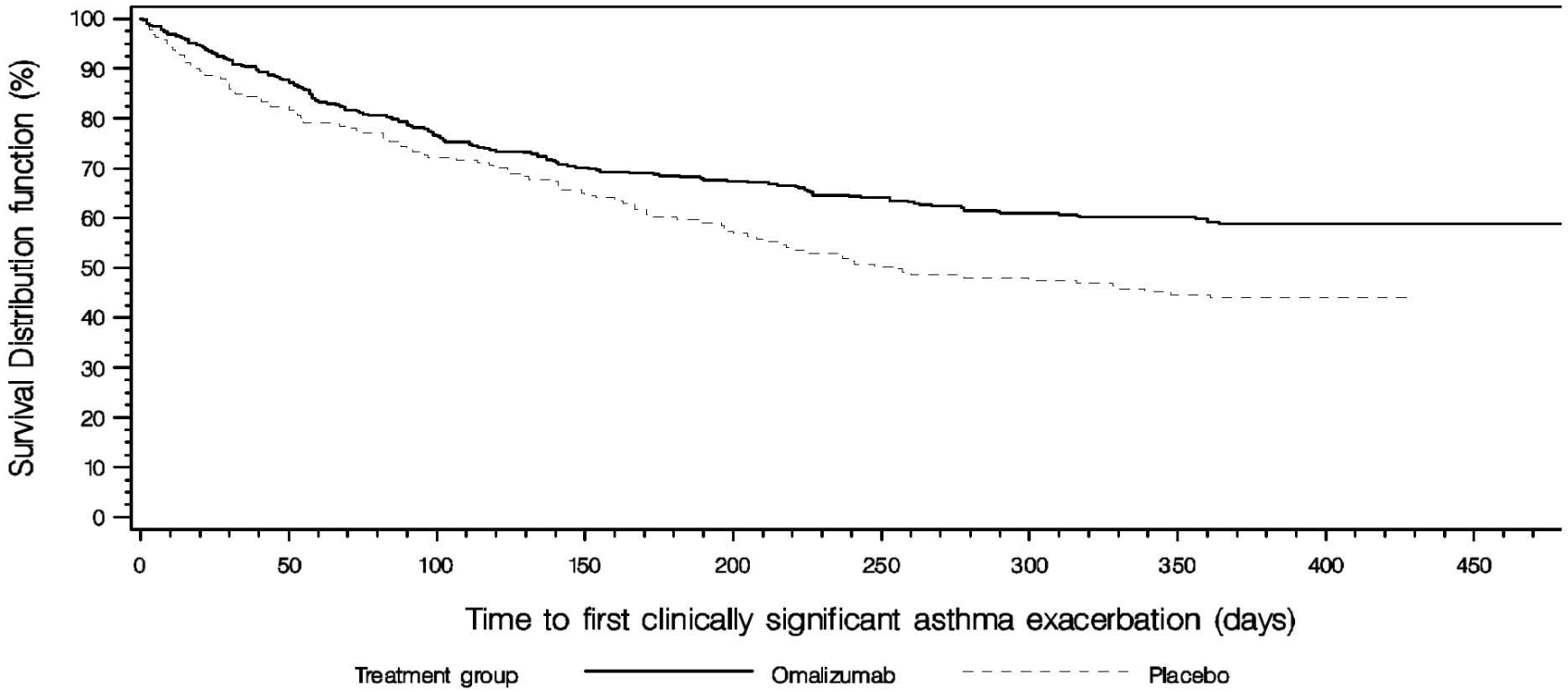
- Age subgroup (6-8, 9-11)
- Gender
- Race
- Country
- US vs non-US
- Baseline IgE
- Baseline IgE and Weight
- Baseline percent predicted FEV1
- Baseline corticosteroid dose
- LABA use
- LABA + ICS dose

IA05: Secondary endpoints, MITT

Secondary variable	Xolair N=384	Placebo N=192	Treatment Comparison	
	Mean	Mean	Difference / Nominal p-value	
Asthma exacerbation rate, 52 wks	0.78	1.36	0.58	**p<0.001**
Nocturnal symptom scores, 24 wks	-0.63	-0.50	0.13	p=0.114
Asthma rescue med use, 24 wks	-1.3	-1.0	0.3	p=0.047
PAQLQ score*, 24 wks	0.92	0.89	0.04	p=0.676
Activities	0.85	0.76	0.09	
Emotions	0.89	0.91	-0.02	
Symptoms	0.99	0.93	0.06	

*PAQLQ = Pediatric Asthma Quality of Life Questionnaire
Minimally Important Difference (MID) for combined PAQLQ score = 0.5

IA05: Time to first asthma exacerbation



Hazard ratio = 0.644 (95% CI of ratio = 0.501, 0.827), Cox proportional hazards model

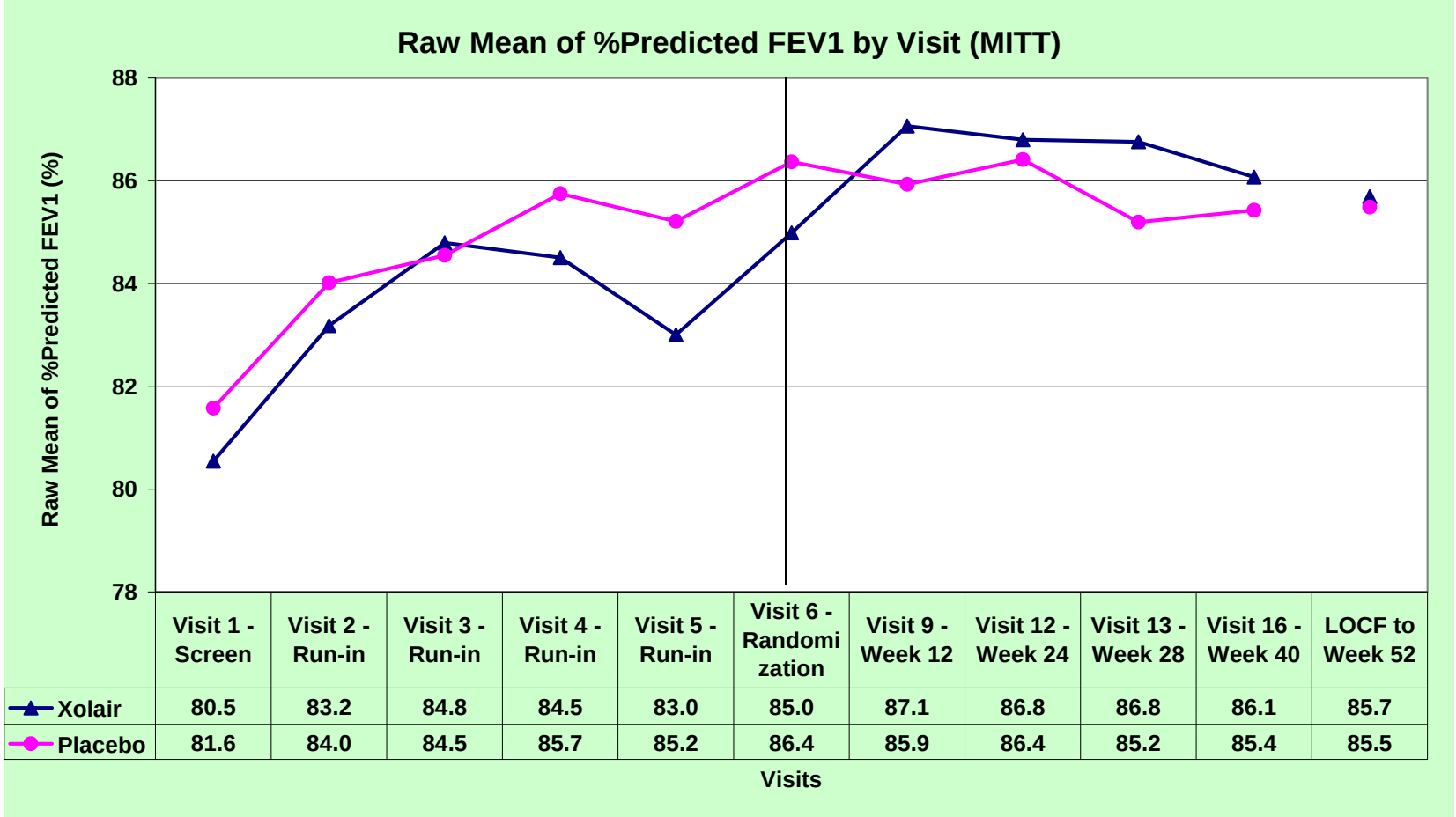
Annualized/Annual exacerbation rates: NNT

Phase / Period	Annualized or Annual Rate			Number Needed to Treat† Patient-Years (95% CI)
	Xolair	Placebo	Rate diff	
Asthma exacerbation rate (primary and secondary endpoints)				
24-week fixed ICS	0.97	1.39	0.43	2.34 (1.30, 11.26)
52-week DB period	0.78	1.36	0.58	1.72 (1.15, 3.42)

†Number Needed to Treat (NNT) is expressed in patient-years.

Patient-years = Number of patients that need to be treated for one year to save one exacerbation, or the number of years that one patient needs to be treated to save one exacerbation.

IA05: Change in percent predicted FEV1, MITT

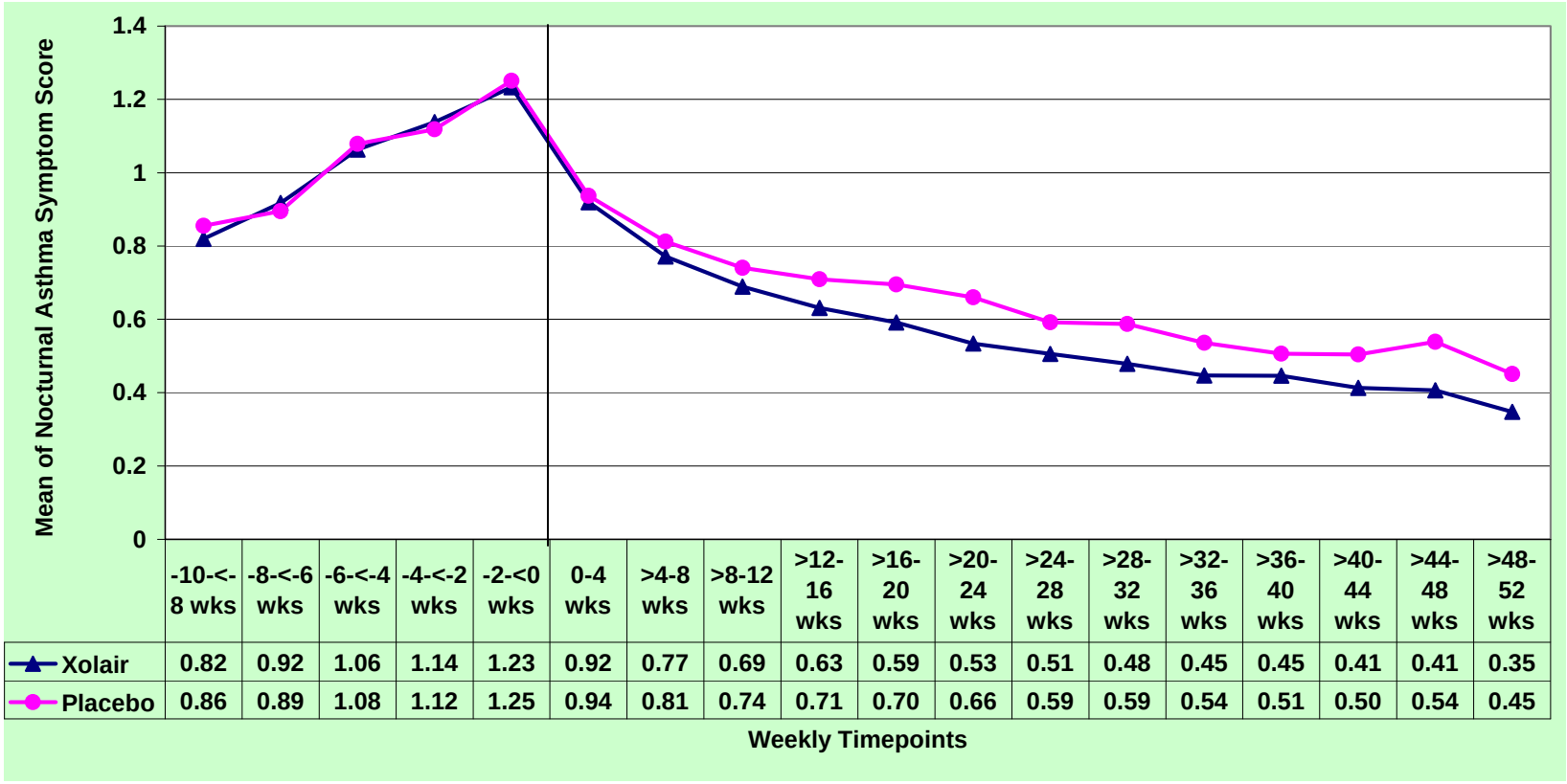


	Visit 1 - Screen	Visit 2 - Run-in	Visit 3 - Run-in	Visit 4 - Run-in	Visit 5 - Run-in	Visit 6 - Randomization	Visit 9 - Week 12	Visit 12 - Week 24	Visit 13 - Week 28	Visit 16 - Week 40	LOCF to Week 52
Xolair	80.5	83.2	84.8	84.5	83.0	85.0	87.1	86.8	86.8	86.1	85.7
Placebo	81.6	84.0	84.5	85.7	85.2	86.4	85.9	86.4	85.2	85.4	85.5

Visits

- LS mean difference in FEV1: @24 weeks: 38.2 mL (95% CI -8.9, 85.4), @52 weeks: 34.7 mL (95% CI -12.9, 82.3)

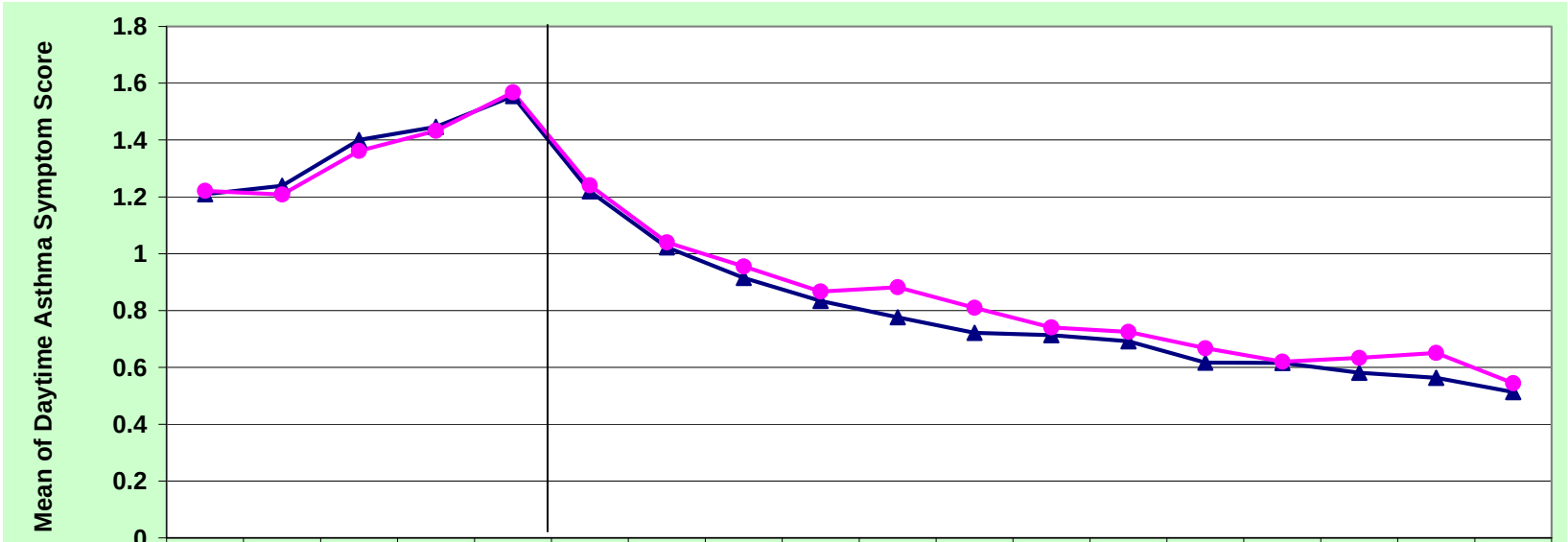
IA05: Nocturnal symptom scores, MITT



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	0.82	0.92	1.06	1.14	1.23	0.92	0.77	0.69	0.63	0.59	0.53	0.51	0.48	0.45	0.45	0.41	0.41	0.35
Placebo	0.86	0.89	1.08	1.12	1.25	0.94	0.81	0.74	0.71	0.70	0.66	0.59	0.59	0.54	0.51	0.50	0.54	0.45

Weekly Timepoints

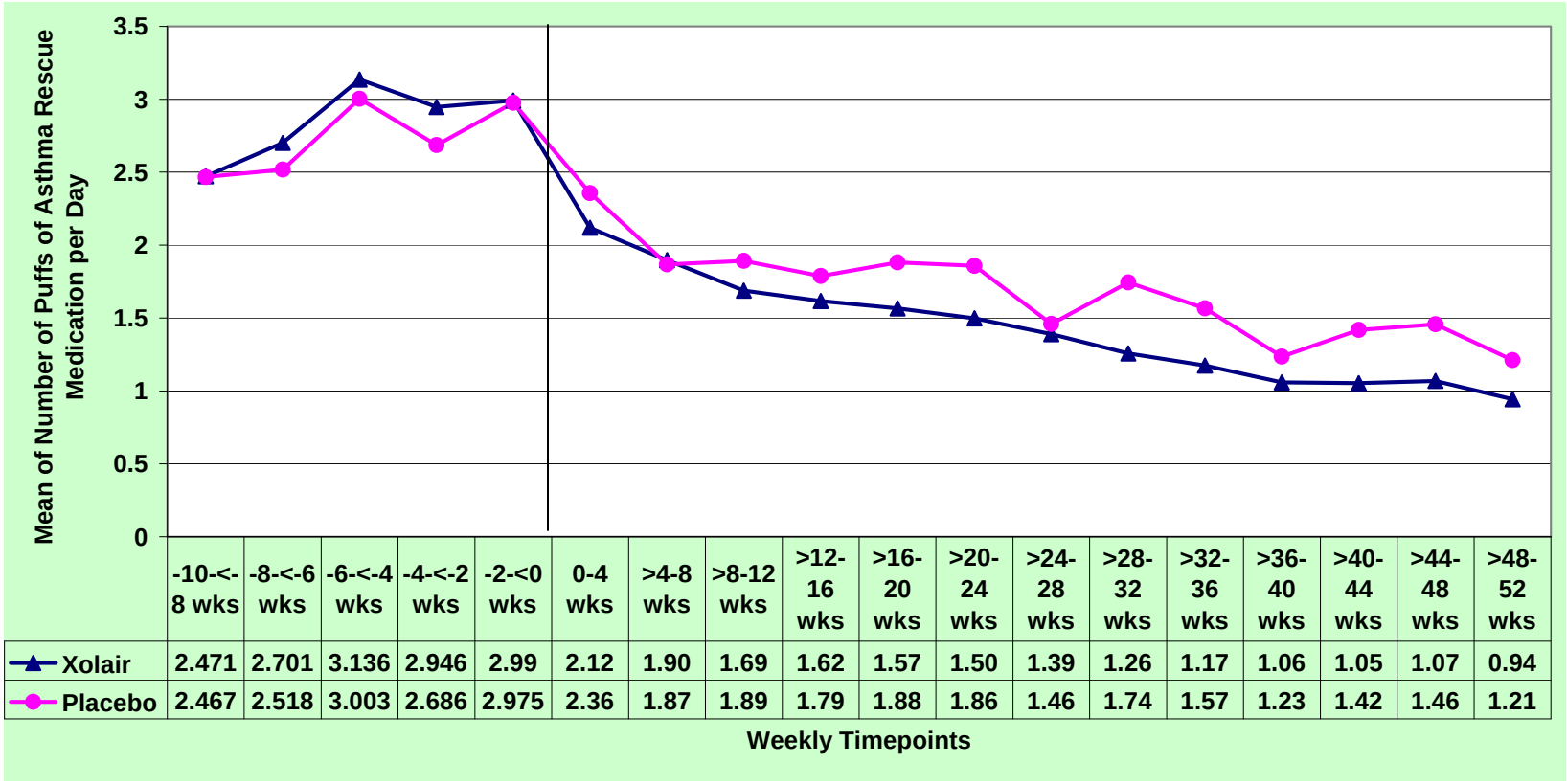
IA05: Daytime symptom scores, MITT



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	1.21	1.24	1.40	1.45	1.55	1.22	1.02	0.91	0.83	0.78	0.72	0.71	0.69	0.62	0.62	0.58	0.56	0.51
Placebo	1.22	1.21	1.36	1.43	1.57	1.24	1.04	0.96	0.87	0.88	0.81	0.74	0.73	0.67	0.62	0.63	0.65	0.54

Weekly Timepoints

IA05: Rescue medication, MITT



	-10-<-8 wks	-8-<-6 wks	-6-<-4 wks	-4-<-2 wks	-2-<0 wks	0-4 wks	>4-8 wks	>8-12 wks	>12-16 wks	>16-20 wks	>20-24 wks	>24-28 wks	>28-32 wks	>32-36 wks	>36-40 wks	>40-44 wks	>44-48 wks	>48-52 wks
Xolair	2.471	2.701	3.136	2.946	2.99	2.12	1.90	1.69	1.62	1.57	1.50	1.39	1.26	1.17	1.06	1.05	1.07	0.94
Placebo	2.467	2.518	3.003	2.686	2.975	2.36	1.87	1.89	1.79	1.88	1.86	1.46	1.74	1.57	1.23	1.42	1.46	1.21

Weekly Timepoints

IA05: Percent change in ICS dose, MITT

ICS dose (mcg)	Xolair N=384	Placebo N=192
	Mean (SD)	Mean (SD)
Baseline	538 (289)	520 (287)
Week 52	517 (303)	522 (312)
Percent change	**-3.6%**	**+1.8%**

Pediatric safety database, 6-11y

Placebo-controlled in asthma (AAP pop)	N
• IA05: Pivotal efficacy and safety	628
• 010Core: Safety study with secondary efficacy	298
Open-label asthma	
• 010E, 010E1: Treatment extensions to 010core	171
• Q2143g (ALTO): Large safety study, primarily in adults and adolescents	128
• ALTO E1 and E2: ALTO treatment extensions	34
Other diseases	
• D01: Allergic rhinitis	100
• 0113: Atopic dermatitis	16

Safety Database

- 1,217 children 6 through 11 years
  - Placebo-controlled asthma studies IA05 and 010core (AAP pop): 926
    - 624 exposed, 583 for 6 months, 292 for 1 year

Demographics	Xolair N=624	Placebo N=302
Age, (yr), Mean	8.8	8.6
6-9y	360 (58%)	192 (64%)
10-11y	264 (42%)	110 (36%)
Male	430 (69%)	201 (67%)
Female	194 (31%)	101 (33%)
Caucasian	398 (64%)	204 (68%)
Black	105 (17%)	42 (14%)
Other	121 (19%)	56 (19%)

Adverse Events (AEs)

- 2 malignancies, both in placebo-treated patients in IA05 / IA05FU
- 2 cases of anaphylaxis, not associated with Xolair treatment
- Asthma exacerbation/hospitalization SAEs in IA05:
  - Omalizumab: 44 events (6 ICU) in 30/421 (7.1%)
  - Placebo: 27 events (3 ICU) in 21/207 (10.1%)
- No differences in targeted adverse events: anaphylaxis*, skin rashes, urticaria, bleeding related disorders, serum sickness syndrome

* Per criteria published by Sampson et al. (2005) JACI 115(3)

Adverse Events (AEs)

- Common AEs
  - Most frequently reported were nasopharyngitis, upper respiratory tract infection, headache, and fever
  - Pneumonia (AAP pop): Xolair 0.5%, Placebo 2.3%
  - Relatively evenly dispersed over time
  - No differences between 2- and 4-week dosing
- Asthma AEs and SAEs in IA05 FU trended to less frequent in patients previously treated with Xolair

Summary: Dosing Rationale/Schema

- Follows adult/adolescent schema (body weight and IgE)
- Assumes relationship of free IgE with cell-bound antigen-specific IgE and asthma symptoms
- In each weight class, pediatric patients with baseline IgE >700 IU/mL receive higher doses of Xolair than adults
- The higher dosing results in circulating omalizumab-IgE immune complexes for patients with baseline IgE levels of ≥500 IU/mL that are greater than levels seen in adults with baseline IgEs up to 700 IU/mL
- Circulating complexes present 4 months after stopping therapy
- The clinical meaning of higher circulating immune complexes is unknown

Summary: Pediatric Program 6-11y

- No evaluation of dose-response
- No studies evaluated Xolair against an arm in which patients were treated with an increase in ICS dose
- No studies evaluated how or when to stop Xolair therapy
- Primary efficacy variable and endpoint
  - Reflects treatment with 3 days of doubled ICS dose or systemic CS
  - Based on investigator judgment
  - Underlying reason (i.e., signs, symptoms, or objective measures) that prompted treatment not captured

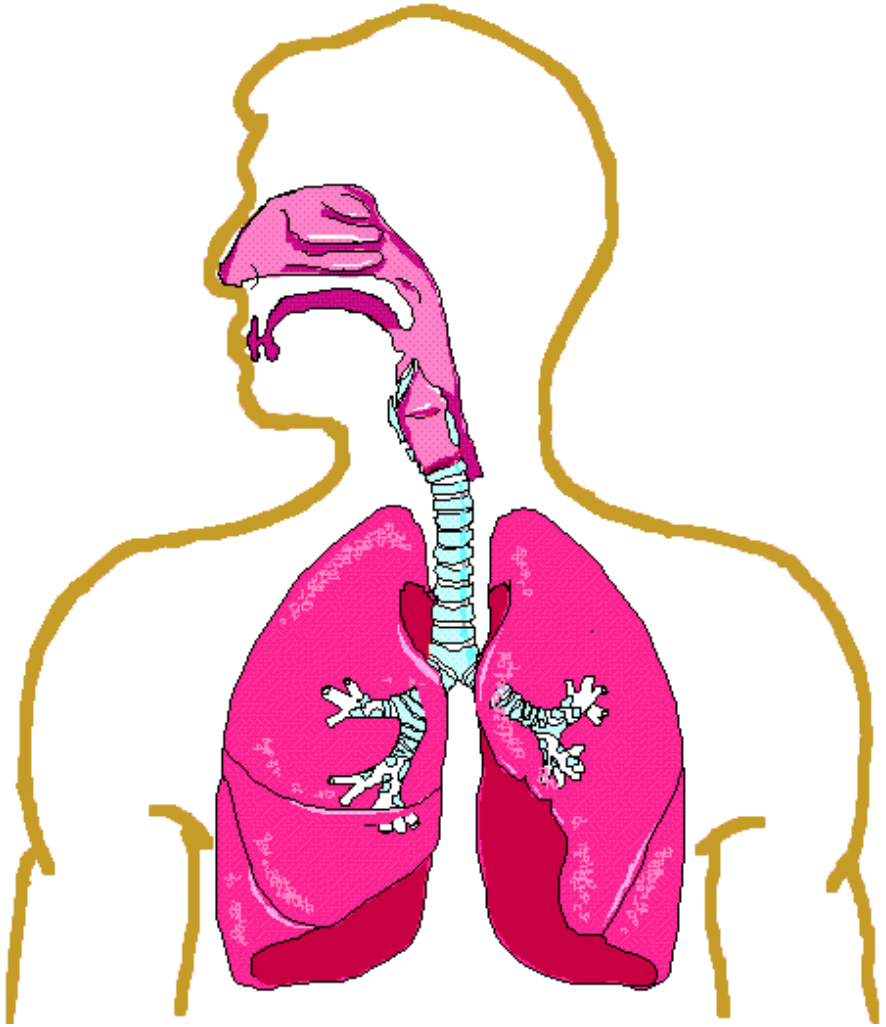
Summary: Efficacy

- Primary endpoint statistically significant, supported by sub-analyses of primary, and the secondary endpoint of exacerbations over 52 weeks
- Efficacy is numerically small and clinically modest
  - Treatment for 2 years and 4 months with 2-weekly or 4-weekly injections of Xolair results in a savings of 1 episode of 3 days of doubled ICS dose or oral CS (NNT=2.34 patient-years)
  - No meaningful effect on other endpoints typical of an asthma controller, such as spirometry measures, rescue medication use, symptoms scores, health care utilization, missed days of school or work, or QOL
  - No effect to reduce ICS dose

Summary: Safety

- Safety population size was sufficient for assessment of common adverse events, but not for malignancy risk
- No safety risks noted in the safety database beyond the risks noted in the adult/adolescent database
- No reason to expect that the risks (e.g., malignancy and anaphylaxis) identified in adults and adolescents would be different in children
- Duration of treatment for children over a life span may be longer

Division of Pulmonary and Allergy Products



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Xolair® (Omalizumab): Review of Post Marketing Malignancy and Drug use data

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Xolair® utilization

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Outline of Presentation

- ***Overview of Benefits***
- ***Overview of Risks***
  - *Clinical trial data (adult & pediatric)*
  - *EXCELS study overview*
  - *Spontaneous (MedWatch) Reports of Malignancies*
- ***Omalizumab Utilization***
- ***Summary and Conclusions***

Overview of Benefits

Summary of treatment benefits (adult studies)

- *Reduction in protocol defined asthma exacerbation rates*
- *Some reduction in ICS use*
- *No clinically significant reduction:*
  - *in oral steroid use,*
  - *improvement in lung function,*
  - *reduction in rescue medication use.*

Overview of Benefits:

Pediatric Clinical Development Program (IA05)

- Treatment with Xolair resulted in protocol defined decrease in asthma exacerbation
- No significant benefits:
  - -Nocturnal asthma symptom scores
  - -Mean number of rescue medications
  - - Lung function
  - - ER visits and hospital admissions

Overview of Risks

Potential risks assessed from:

- Clinical trial data (adult & pediatric)
- EXCELS study overview
- Spontaneous (MedWatch) reports of malignancies

Overview of Risk

Areas of concern / focus

1. **Anaphylaxis**
   1. ***0.2 % of patients***
   2. ***Labeled***
2. **Malignancy**
   1. approved with a label warning for malignancy and PMC study to assess potential risk of malignancy (EXCELS)
3. **Cardio-vascular (CV) Events**
   1. **New signal, review pending**

Clinical Trial and Malignancy Signal

- **Studies suggest higher omalizumab rate:**
  - **0.5% vs 0.2%**
  - **6.3 vs 3.3 events/1000 pt yrs**
  - **Throughout study exposure periods**
  - **SEER comparisons:**
    - **-higher rate for omalizumab**
    - **-lower rate for control**

Omalizumab and Malignancy adult clinical trials

	Xolair® n= 4127	Control n= 2236
Any event	20 (0.5%)	5 (0.2%)
Skin, non-M	5	3
Breast	5	0
Prostate	2	0
Melanoma	2	0
Parotid	2	0
Other	5	2

Xolair® and Malignancy

- Summary Safety from Pediatric supplement (IA05)
  - No malignancy in omalizumab treated cohort (n= 624)
  - Two cases in control (n=302)
    - ✓ medulloblastoma and renal cell
  - No report of death during study period
  - Single case of anaphylaxis in each treatment group

Omalizumab and Malignancy

EXCELS study

- Prospective, 5 year observational cohort study
- 5000 omalizumab - treated and 2500 untreated
- Objective: To determine incidence of malignancies and other serious adverse events
- Study initiated: June, 2004
- Total enrollment: 7951
  - 5041 omalizumab cohort
  - 2886 non-omalizumab cohort
- Expected study completion: 2011/12

Omalizumab and Malignancy

EXCELS Study: Limitations & conduct issues

- A number of limitations and concerns:
  - ✓Non-Randomized, Observational study design
  - ✓Patient recruitment and retention
  - ✓Patient selection criteria
  - ✓ Variable duration of exposure
- These limitations may result in a negative study or in underestimation of risk

Spontaneous Reporting

- AERS database: Computerized database containing > 4 million reports
- Spontaneous reporting
  - Not required of health care providers
  - Sponsor required to report any adverse events of that they are aware
- Strengths
  - Detection of rare but serious adverse events
  - Descriptive case series

Spontaneous Reporting

- Limitations
  - Lower utility for expected events in an at-risk population (e.g. renal failure, MI, CHF in adults)
  - Underreporting
  - Biases in reporting
  - Quality of reports
  - Causality assessment difficult for events with long latency and high background rates

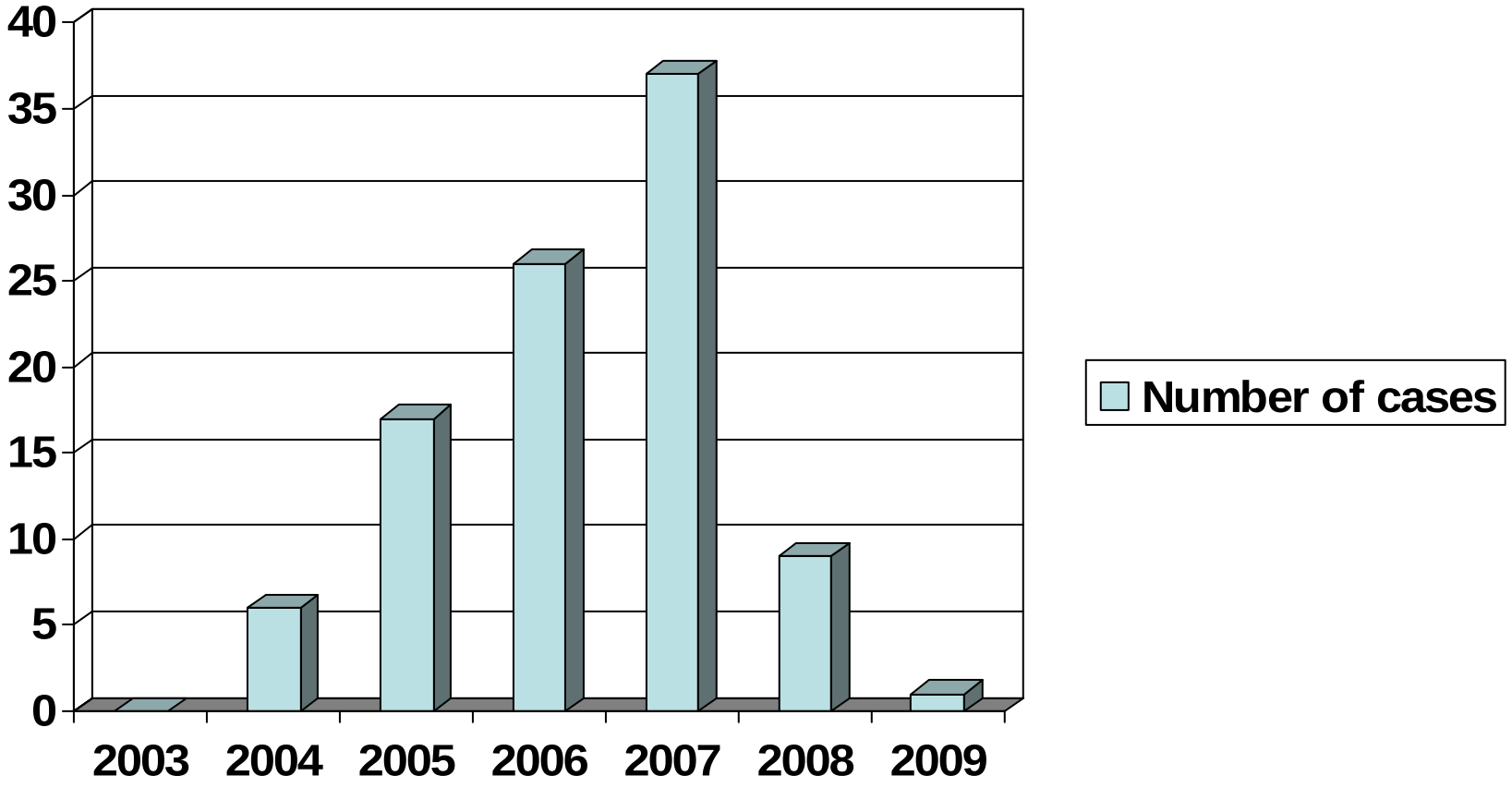
Malignancy reports

- Search data : 6/20/2003 through 2/8/2009
- Search Terms: System Organ Class (SOC), Neoplasm benign, malignant and unspecified
- **Results**:
  - ✓ 118 total reports (crude counts)
  - ✓ 3 duplicate reports
  - ✓ 19 cases excluded (miscoding, unable to confirm diagnosis or if tumor is benign or malignant
  - ✓ ***96 cases presented***

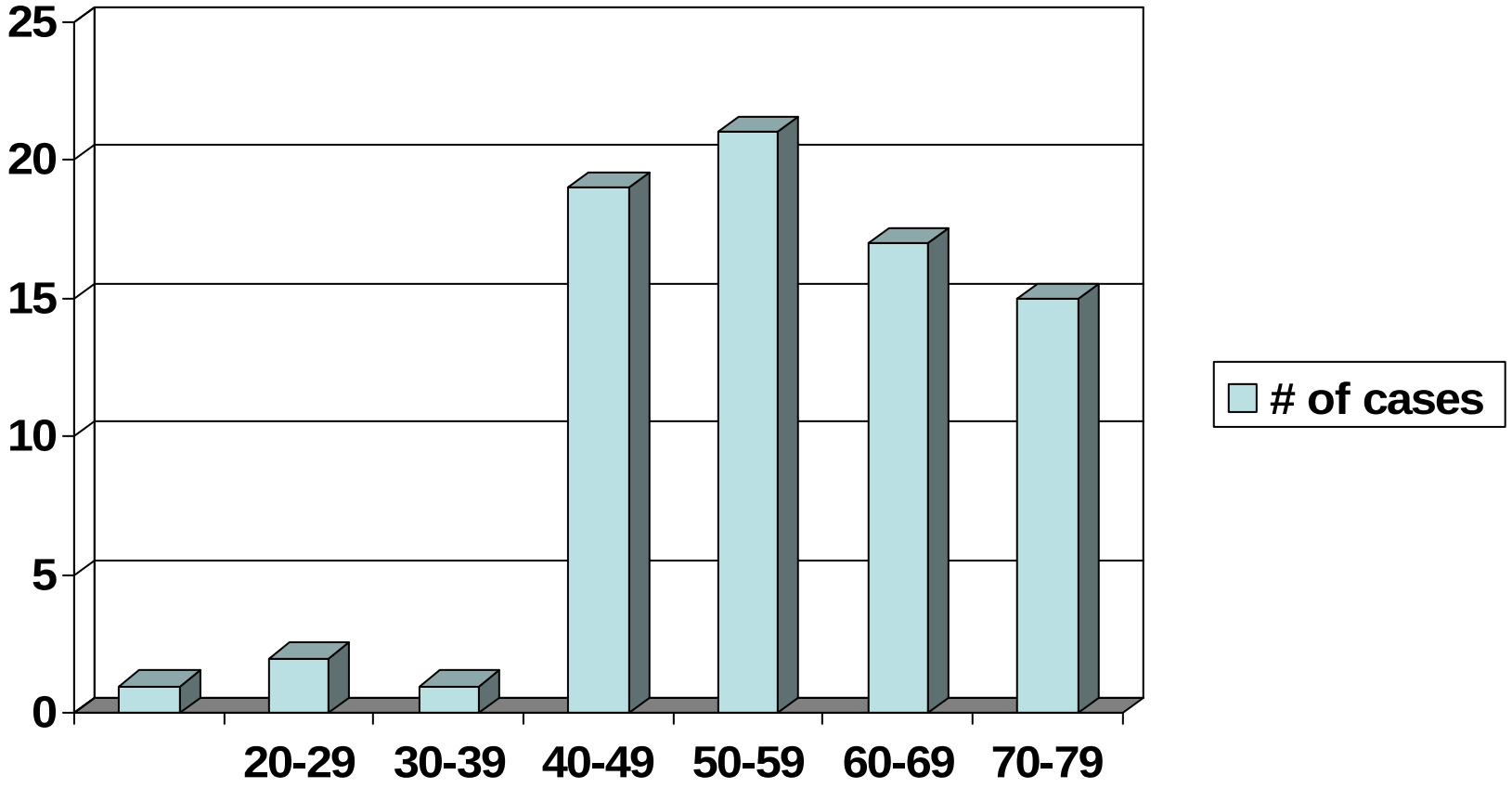
Characteristics of malignancy cases

Number of cases	n= 96
Age : Range (Yrs)	13-76
Gender Male Female Unknown	 31 58 7
Duration of TX (Months)	Range 2-42; Average 14; Median 10
Report source	Domestic 86; Foreign 10
Reporter	health care 76; consumer 20

Malignancy cases: # of reports/ year



Malignancy cases: age distribution



Frequency of Common Cancers* Reported with Xolair
- by Organ System and Reported Cancer Site and Number of Cases, N=78
From U.S. approval on 20Jun03 through 18Feb09

Organ System	Reported Cancer Site	Number of Cases
Breast	Breast	25
Digestive	Colon	6
Endocrine system	Thyroid	4
Genital System	Prostate	7
Leukemia	Leukemia	2
Lymphoma	Non-Hodgkin Lymphoma	5
Respiratory System	Lung	16
Skin	Melanoma	5
	Non-melanoma	2
Urinary system	Bladder	2
	Renal	4

* To qualify as a common cancer, the estimated annual incidence for 2009 had to be 35,000 cases or more. (www.cancer.gov)

Frequency of Less Common Cancers* Reported with Xolair
- by Organ System and Reported Cancer Site and Number of Cases, N=18
From U.S. approval on 20Jun03 through 18Feb09

Organ System	Reported Cancer Site	Number of Cases
Bone	Bone	2
Digestive	Liver	1
	GIST	1
NervousSystem	Brain	2
	Anaplastic astrocytoma	2
Genital System	Ovarian	3
Myeloma	Multiple myeloma	3**
Lymphoma	Hodgkin Lymphoma	2
Oral Cavity	Tongue	1
Eye & Orbit	Eye	1

**Highly probable that the 3 reports of myeloma occurred in the same patient

* To qualify as a common cancer, the estimated annual incidence for 2009 had to be 35,000 cases or more. (www.cancer.gov)

Malignancy cases series: Conclusion

- Case series did not reveal any unique malignancies or clusters
- Reported malignancies similar to those observed in the Clinical trial
- These cases by themselves can not establish an increase risk due to limitations of spontaneous reporting

Malignancy cases series: Conclusion

The reported cases can't be discounted

- Relatively higher reports compared the limited drug use
- Malignancy labeling for may discourage reporting
- Observational study reports of decreased cancer risk in asthmatics
- Hypothesis that IgE may play a tumor surveillance role

Stepwise asthma treatment guidelines

- *2007 National Heart, lung and Blood Institute (NHLBI) Expert Panel Report 3**
  - Xolair is a consideration at step 4, and is recommended in steps 5 and 6

- *GINA (Global Initiative for Asthma)***
  - Anti-IgE as an add on to poorly controlled Step 5 asthmatics

*http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

**http://www.ginasthma.org/Guidelineitem.

Xolair® Utilization

- Drug use data requested to analyze the manner of its use (Consistent with national and International guidelines?)

- Assess the extent (if any) of inappropriate use

Omalizumab Utilization:
Databases descriptions

- The IMS Health, IMS National Perspectives™

  used to determine the various retail and non-retail channels of Xolair® distribution in terms of number of packages of products sold

- Wolters Kluwer's Health Source® Lx database

  a longitudinal patient data source which captures adjudicated claims across the United States. The database contains a mix of prescription claims from commercial plans, Medicare Part D plans, Cash and Medicaid claims

- SDI, Physician Drug & Diagnosis Audit (PDDA)

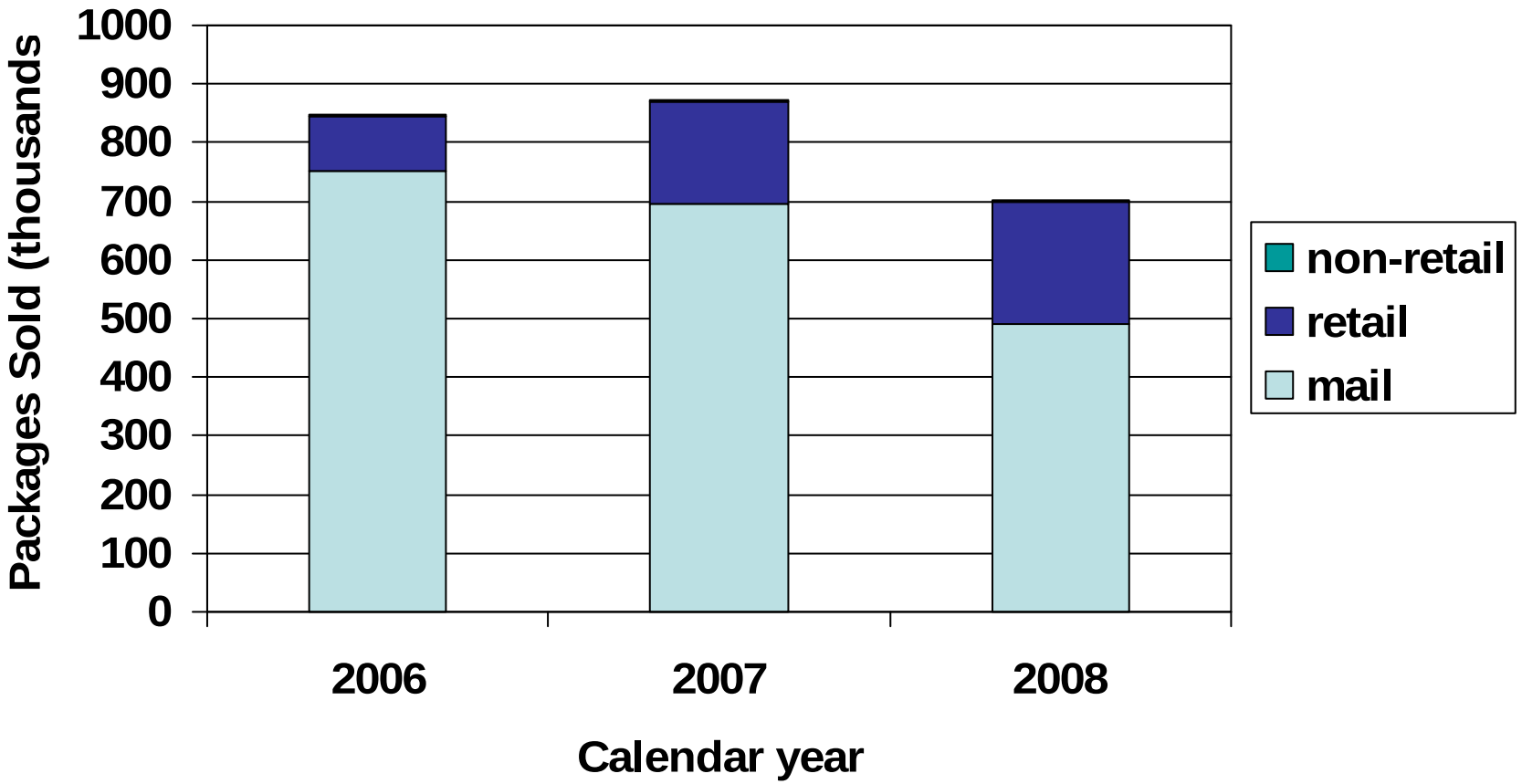
  a nationally projected monthly survey of 3,200 office based physicians designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S.

Absolute utilization

- Analysis of physicians office survey for year 2008 includes mention of Xolair® in 0.2% of office visits for asthma

- Suggests very limited market presence

Nationally projected wholesale distribution of Xolair vials, by pharmacy type

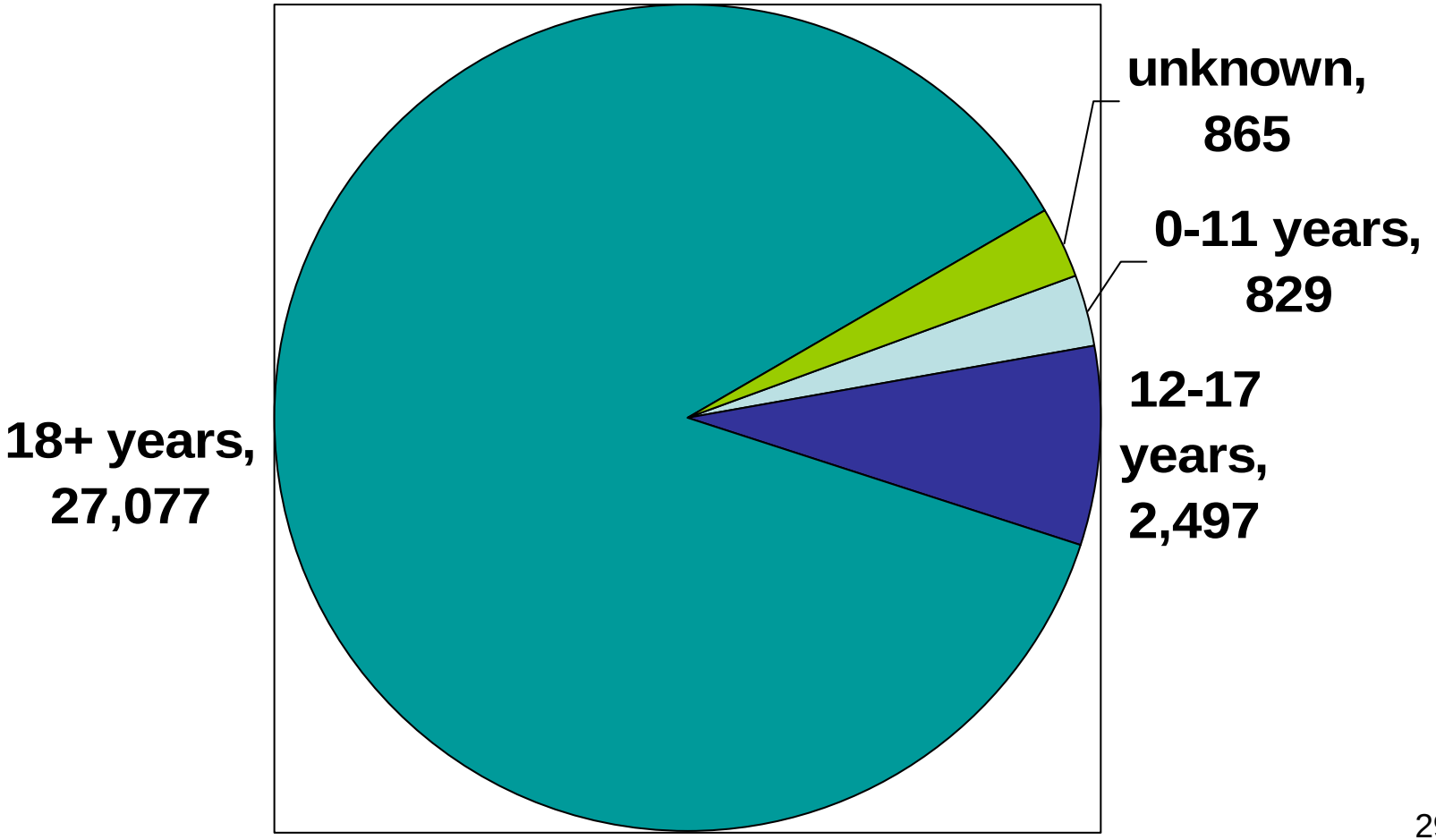


Source: IMS Health, IMS National Sales Perspectives, Retail and Non-Retail
Data Extracted 5/2009

Xolair® Utilization: Method

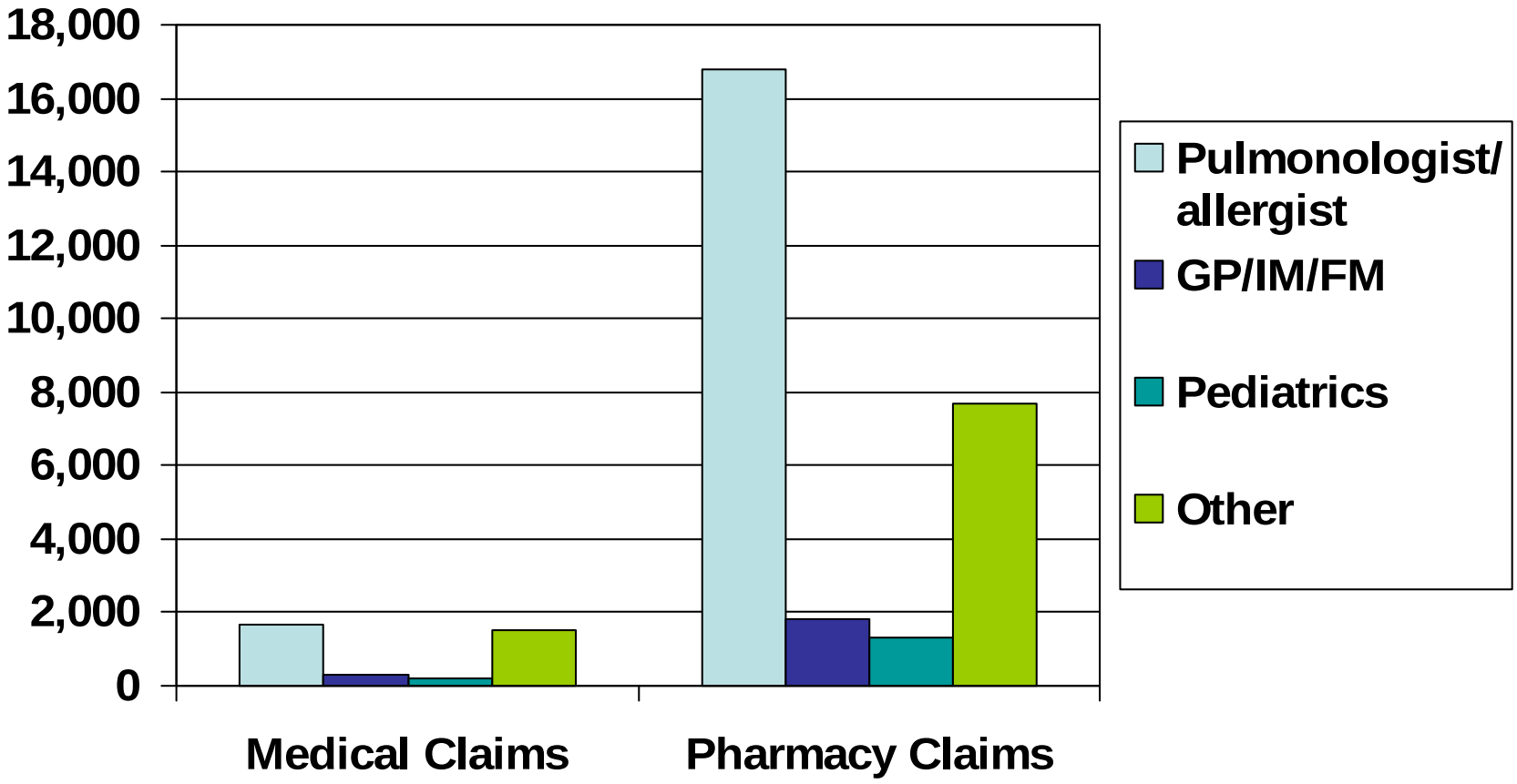
- From the Wolters Kluwer database, unprojected patient demographic data and physician specialty information for years 2002-2008 was obtained
  - Multiple asthma drug class dispensing analysis was conducted for year 2008
  - Patients where stratified as mild, moderate or severe based on the use of Xolair® alone or with other asthma medications
- To corroborate the findings, data on concurrent drug use was obtained from a survey of office-based physicians from the SDI, Physician Drug and Diagnosis Audit (PDDA) for years 2006-2008

Patient age for Xolair medical and pharmacy claims for years 2002 - 2008



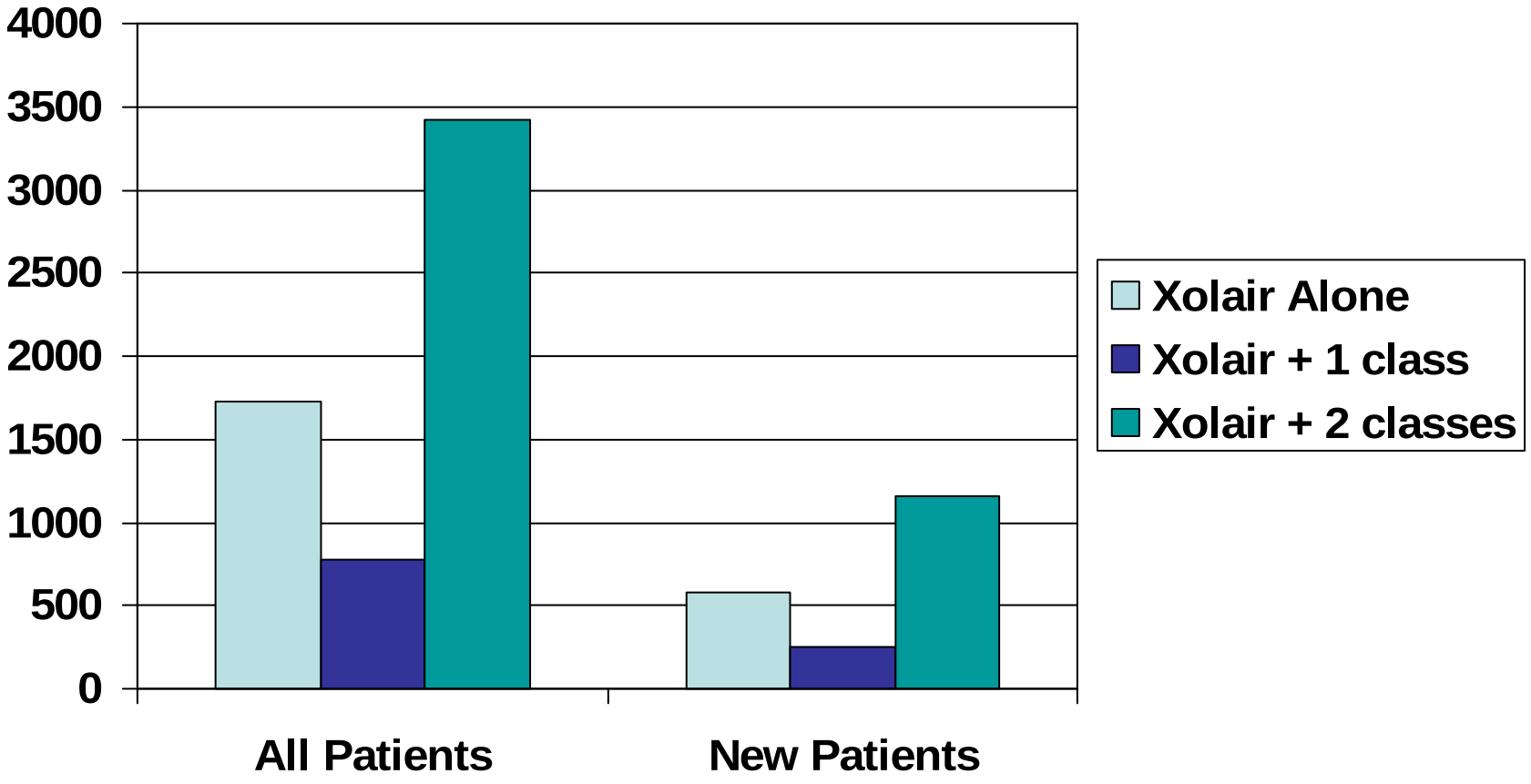
Source: Wolters Kluwer Health Source® Lx, Data Extracted 5/2009

of patients with a medical or pharmacy claim by physician specialty 2002-2008



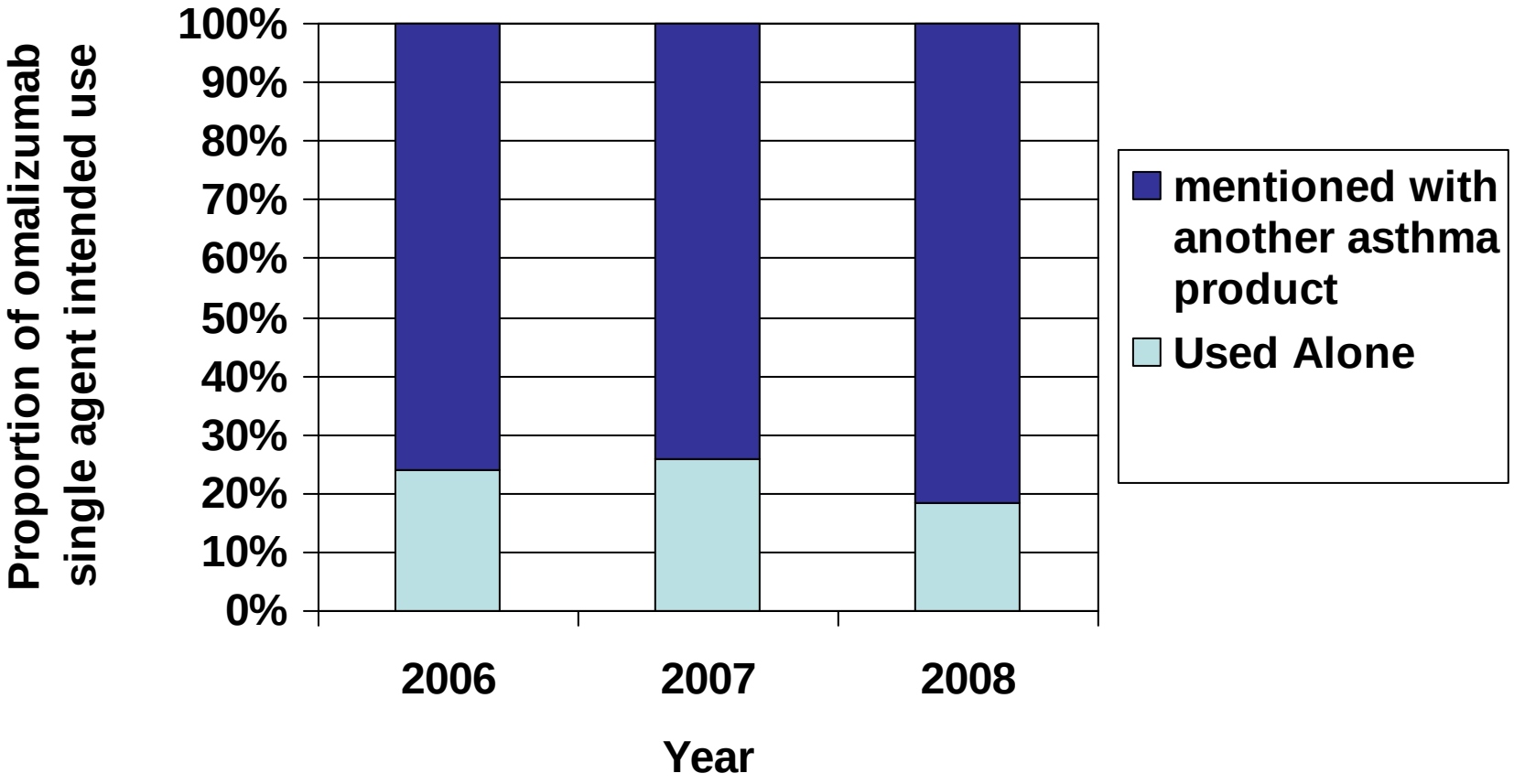
Source: Wolters Kluwer Health Source® Lx, Data Extracted 5/2009

Xolair patient classification based on number of asthma products received during 2008



Source: Wolters Kluwer Health Source® Lx, Data Extracted 5/2009

Survey of omalizumab use by outpatient physicians, 2006-2008



Drug Utilization summary

- Data from Wolters Kluwer estimated that approximately 80% of patients were 18 years or older
- 29% of patients in this sample did not receive another asthma drug product in year 2008
- For year 2008: 13% appear to receive a single class of asthma medication along with Xolair®
- Physician survey (2006-2008) indicated that approximately 18-25% of the time Xolair® was used without another asthma product

Drug Utilization summary

Based on the drug use data analysis

- 42% (29% +13%) of Xolair recipients appear to be mild asthmatics
  - ➢ It appears that Xolair® may be used outside its approved indication and outside national recommendations
- The data suggests that some patients receiving Xolair® (mild asthmatics) where the drug failed to show efficacy
  - ➢ Suggestion of mis-use or inappropriate use

OSE Conclusions

- Limited to protocol defined reduction in asthma exacerbation
- Defined risk for anaphylaxis
- Malignancy: Magnitude of risk poorly characterized in both adults and pediatric population
- CV: New signal (Pending further assessment and characterization)
- Some evidence of drug use outside guidelines for sub-population asthmatics with limited benefit

Pediatric Risk/Benefit Assessment
Xolair® (omalizumab)

Nov 18, 2009

Hari Cheryl Sachs, MD
Team Leader
Pediatric and Maternal Health Staff
Office of New Drugs

Outline

- Epidemiology and impact of asthma in children
- Asthma controllers in Children
- Summary evaluation of studies of Xolair® in children
  - Efficacy
  - Safety
- Related opinion of omalizumab use in literature
- Risk/benefit considerations

Asthma in Children*

- Over 10 million children (14%) ever diagnosed with asthma
- ~7.0 million (9.4%) children currently have asthma
- Mortality rate lower than adults:
  <15 years of age : ~ 0.2/100,000
  Ages 25 to 75: ~ 0.5 to 2.3/100,000
- ER visits: rates higher than adults
  ~1/100 (<18 years) vs. 0.47/100 (>18 years)

*CDC FASTSTATS 2006

Asthma in Children

Impact on Individual:

- Quality of Life
- School Attendance
- Physical activity and Sports Participation
- Peer interaction

Asthma Controllers for Children 6-11 y

Corticosteroids (inhaled and nebulized)

Leukotriene modifiers (montelukast and zafirlukast)

Long acting beta-agonist (salmeterol)

Methylxanthines (theophylline)

Cromolyn sodium

Stepwise Approach for Managing Asthma in Children 5 to 11 Year of Age

Intermittent Asthma

Persistent Asthma: Daily Medication
Consult with asthma specialist if Step 4 care or higher is required.
Consider consultation at Step 3.

Step 1
Preferred:
SABA PRN

Step 2
Preferred:
Low-dose ICS
Alternative:
Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred:
EITHER
Low-dose ICS + either LABA, LTRA, or Theophylline
OR
Medium-dose ICS

Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA or Theophylline

Step 5
Preferred:
High-dose ICS + LABA
Alternative:
High-dose ICS + either LTRA or Theophylline

Step 6
Preferred:
High-dose ICS + LABA
Alternative:
High-dose ICS + either LTRA or Theophylline

Step up if needed
(first check adherence, inhaler technique, environmental control, and comorbid conditions)

Assess control

Step down if possible
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.
Step 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes)

Quick Relief Medication for All Patients
- SABA as needed for symptoms, intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Caution: Increasing use of SABA or use ≥ 2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Source: National Heart Lung and Blood Institute: Guidelines for the Diagnosis and Management of Asthma (EPR-3)

AE profile of Controller Agents

Corticosteroids (CSS): HPA axis suppression, Cushing's, Immunosuppression

Leukotriene modifiers: neuropsychiatric adverse events

LABA's: Boxed warning: increased risk asthma-related death

Theophylline: exacerbation of peptic ulcer, seizure, cardiac arrhythmias

Cromolyn sodium: eosinophilic pneumonia

Xolair® - Efficacy Findings

- Statistically-significant benefit in primary end-point rate of exacerbations (protocol-defined)
- No consistent effect on supporting secondary end-points
  - Steroid-sparing effect, diminished use of rescue medications, rate of medical encounters, asthma symptoms
- Clinical relevance unclear as rate of exacerbations low
  - No exacerbations: 64 % Xolair vs. 58% Placebo
  - Number needed to treat: 2.34 (1.30, 11.26) Patient-Years

Xolair® - Safety Findings

- Short-term data demonstrates Xolair® is well-tolerated in children 6 to 12 years old
- Two cases each of anaphylaxis and malignancy, not related to omalizumab
- Asthma Safety Database (n = 926; 624 exposed during placebo-controlled trials)
  - 1 year exposure (n= 292)
  - 6 month exposure (n= 583)

  Note: number treated may not be sufficient to detect anaphylaxis or malignancy if rates in children similar to adults

Safety Signals in Adults

- Malignancy (0.4 % vs. 0.2% controls)
- Anaphylaxis (0.2%)
- Potential Cardiovascular signal
  - Early communication: disproportionate increase in cardiovascular and thrombotic AE's
  - EXCEL study ongoing

Relevant Literature/Opinion

Efficacy

- Limited data: general consensus in the literature and in evidenced-based medicine recommendations/guidelines support the current, approved indication of omalizumab

  NAEPP/NHLBI 2007 Guidelines

- Asthma prevalence and IgE (Gergen 2006)
  - Total IgE associated with asthma in atopic patient
  - Allergen-specific IgE levels more predictive
  - “Significant portion of asthma in population exists independent of IgE levels”

Relevant Literature/Opinion

Duration of Therapy with omalizumab

- No data to inform labeling
- Ill-defined in literature

Safety

- No novel adverse events, apart from clinical trial data
- Theoretical discussions of potential association with IgE, atopy and malignancy

Pathophysiology of Malignancy and Atopy

- Inverse-relationship between atopy (IgE expression) and cancer risk
- Implications for omalizumab use to impact inverse-relationship unfavorably
- Ultimately, association is only theoretically understood and observationally studied at this time

Summary: Risk/Benefit Considerations in Children

- Asthma cause of serious morbidity
- Existing treatments without malignancy risk
- Limited therapeutic benefit with questionable clinical relevance
- No identified significant safety signal in children, to date [however small numbers]
- Dosing requires injection; risk of anaphylaxis 2/1000
- Unanswered questions: treatment duration, omalizumab-IgE immune complexes
- Potential cardiovascular signal (EXCEL)
- Malignancy risk in adult trial data

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US Food and Drug Administration

Meeting of the Pulmonary-Allergy Drugs Advisory Committee

November 18, 2009

Lydia Gilbert-McClain, MD
Deputy Director, Division of Pulmonary and Allergy Products,
Office of New Drugs,
Center for Drug Evaluation and Research,
US Food and Drug Administration

Objective

- To discuss data submitted by the Applicant to support the safety and efficacy of Xolair for the treatment of asthma in patients 6 to 11 years of age with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids

Question 1 - Discussion

Xolair dosing is based on serum IgE levels. Discuss the implications (if any) of dosing that could result in an increase in circulating levels of omalizumab-IgE immune complexes in patients with IgE levels above 500 IU/mL.

Question 2 - Voting

Do the data provide substantial and convincing evidence that Xolair provides a clinically meaningful beneficial effect for the treatment of asthma in pediatric patients 6 to 11 years of age inadequately controlled despite the use of inhaled corticosteroids?

a) If not, what further efficacy data should be obtained?

Question 3 - Voting

Has the safety of Xolair been adequately assessed for the treatment of asthma in pediatric patients 6 to 11 years of age?

a) If not, what further safety data should be obtained?

Question 4 - Voting

Do the safety and efficacy data provide substantial and convincing evidence to support approval of Xolair for the treatment of asthma in patients 6 to 11 years of age with moderate to severe persistent asthma whose symptoms are inadequately controlled with inhaled corticosteroids?

a) If not, what additional information is necessary to support approval?